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Blood Flow to the Forearm and Calf. I. Vasomotor Reactions: Rôle of the Sympathetic Nervous System. ROBERT W. WILKINS AND L. W. EICHNA 425

Blood Flow to the Forearm and Calf. II. Reactive Hyperemia: Factors Influencing the Blood Flow during the Vasodilatation Following Ischemia. L. W. EICHNA AND ROBERT W. WILKINS 450

Blood Flow to the Forearm and Calf. III. The Effect of Changes in Arterial Pressure on the Blood Flow to Limbs under Controlled Vasodilatation in Normal and Hypertensive Subjects. ROBERT W. WILKINS AND L. W. EICHNA 477

Blood Flow to the Forearm and Calf. IV. Thyroid Activity: Observations on the Relation of Blood Flow to Basal Metabolic Rate. L. W. EICHNA AND ROBERT W. WILKINS. 512

A Rapid Method for the Determination of Diodrast-Iodine in Blood and Urine. LOUIS K. ALPERT, M.D. 522

Changes Induced in Patients with Hyperthyroidism by the Oral Administration of Desiccated Thyroid. WILLIAM FRANCIS RIENHOFF, JR. 538

Book Reviews 543

Index to Volume LXVIII 548

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BLOOD FLOW TO THE FOREARM AND CALF*

I. Vasomotor Reactions: Rôle of the Sympathetic Nervous System[1]

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From the Department of Medicine of The Johns Hopkins University School of Medicine

Submitted for publication April 25, 1941

It is known that vasomotor reactions in the forearm and calf differ from those in the hand and foot mainly in three ways: (a) The blood flow to the muscular parts is less influenced by changes in body warmth (1, 2). (b) Some stimuli which produce marked vasoconstriction in the hand or foot may cause only slight or no vasoconstriction in the forearm or calf (1, 3, 4). (c) Some stimuli which produce vasoconstriction in the hand and foot may cause vasodilatation in the forearm and calf (1, 3, 4).

* The four papers in this series, all dealing with measurements of blood flow in the forearm and calf, describe experiments which were undertaken in a broad study of the peripheral circulation in cases of essential hypertension. It is a matter of great importance to know whether the increased peripheral resistance to blood flow in cases of hypertension is due to an irreversible type of change in the walls of the arteries. Likewise, it is desirable to have more information concerning the rôle of the sympathetic nervous system in regulating the peripheral resistance to blood flow in both normal and hypertensive subjects. The plethysmographic method employed in this study has been used previously by other workers in this field (see Paper III (16)), but the results have been difficult to analyze owing to the lack of essential information concerning the limits of accuracy of the method. Therefore, it was necessary first to establish the limitations of the plethysmographic method, and to determine the effect of a variety of influences upon the blood flow as measured by this method (Papers I and II). The effect of changes of arterial pressure on the blood flow in both normal and hypertensive individuals was then investigated (Paper III). The studies of the influence of the basal metabolic rate upon the blood flow (Paper IV) are related to the main problem only in so far as they throw light upon the significance of plethysmographic measurements of blood flow in the forearm and calf.

[1] Supported by a grant from The Commonwealth Fund for the study of essential hypertension.

The rôle of the sympathetic nervous system, and of certain chemical substances, notably epinephrin, in the vasomotor reactions of the forearm and calf has been suggested but not conclusively demonstrated (1, 2, 5). The purpose of the present investigation was to inquire further into the factors influencing these reactions, and especially into the part played by the sympathetic nervous system.

METHODS

Measurements of blood flow (6) and of volume changes in the forearm and calf were made by means of segment plethysmographs (Fig. 1). The limb was fitted with light rubber diaphragms, which were attached to the skin with rubber cement, one just below the elbow or knee, and the other 6½ inches distal to the first. The limb was then placed in the plethysmograph, and the diaphragms, after being attached to the plethysmograph, were backed by hard, fibre-board plates shaped exactly to fit the contours of each limb. Beyond these plates the ends of the plethysmograph were rigidly fixed by metal iris diaphragms supported by screw clamps. This arrangement was so rigid that it was able to withstand a pressure within the plethysmograph of 300 mm. Hg. That it did not significantly obstruct the venous outflow was shown in each experiment by the fact that a pressure always less than 15 mm., and often less than 10 mm. Hg, in the cuff proximal to the plethysmograph was sufficient to cause an increase in limb volume.

The water in the plethysmograph was maintained at 32°C. and gently circulated by a motor-driven stirrer. Recording was effected by air conduction to a Brodie's bellows of 40 cc. capacity. The bellows was equipped with a special hinged writing-lever which moved in a straight vertical line on the smoked drum instead of in the usual arc (Fig. 1). This lever permitted a more uniform calibration by compensating for the decrement which occurs at the top of the arc of the ordinary writing-lever.

During all measurements the subjects lay supine in bed with the head elevated 5 to 10 degrees. The segment in the plethysmograph was at heart level. The circulation to the hand or foot distal to the plethysmograph was occluded, in order to eliminate the effects of vasomotor reactions in those parts upon the blood flow to the segment within the plethysmograph (1, 3).

Skin temperature was measured in the free extremities by means of thermal junctions applied lightly to the skin with adhesive tape. Points on the forearm or calf, removed from the superficial veins, and the pads of the digits were selected for these measurements. Body temperature was measured by a thermal junction inserted at least 5 cm. above the internal rectal sphincter. The galvanometer allowed the detection of changes of 0.1°C. The room was maintained at a temperature as near as possible to 20°C., usually within ±1°C.

Warming of the body to induce reflex vasodilatation was accomplished by placing blankets and electric heating pads on the subject. This was supplemented by

immersing a free limb in water at 45°C. when a quick effect was desired. Generalized reflex vasodilatation was regarded as secured only when both the toes and fingers had warmed to 33 to 35°C. Sweating was found to be an unsatisfactory criterion of vasodilatation; in some subjects it was profuse before significant increases had occurred in the temperature of the toes.

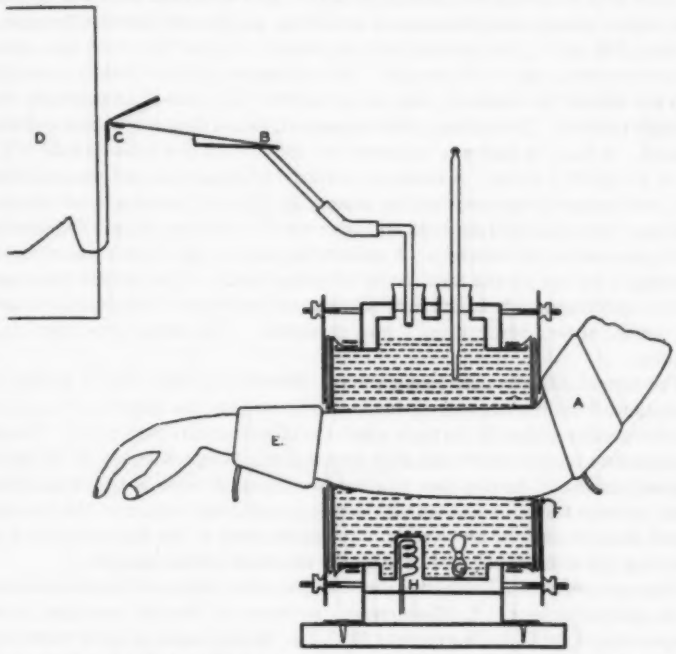

FIG. 1. Diagram of segment plethysmograph for the forearm or calf. *A* is the proximal blood pressure cuff; *B* the Brodie's bellows, equipped with special hinged writing-lever *C*; *D* the recording drum; *E* the distal blood pressure cuff; *F* the fibre-board plate; *G* the stirrer; *H* the heater.

Measurements were begun after the subject had been lying quietly for one hour. The amount of blood flow to the resting forearm or calf was determined every 30 seconds by recording the increase in limb volume which occurred when the venous outflow was obstructed for 15 seconds. During each determination of blood flow the arterial pressure was measured in a free extremity by the usual auscultatory method using a wide cuff and a mercury manometer. The pulse rate was counted from the plethysmographic tracings.

The subject was requested to close his eyes and relax. Control measurements were taken for 3 to 5 minutes before any stimulus was applied. Several stimuli were then given in an attempt to produce transient vasomotor reactions in the forearm and calf. These included ice, pin prick or pinch to indifferent skin areas; a deep breath; immersing a hand or foot in very cold, or very hot, water; exercise of a limb with its circulation occluded; a sudden, loud noise; and mental arithmetic. The various stimuli were administered as follows: Ice, in a block with a flat surface of about 100 sq. cm., was placed firmly in contact with the skin of the face, chest, or a free extremity for 5 to 10 seconds. A sharp pin was quickly pricked repeatedly into the skin of the forehead, neck or extremity. The skin of an extremity was strongly pinched. The subject, when requested, took a deep inspiration and then relaxed. A hand or foot was immersed for one minute in a basin of cold (4°C.) (7) or hot (50°C.) water. A forearm, to which the circulation had been occluded for 1 to 3 minutes, was exercised by having the subject squeeze a blood pressure bulb once a second until he could no longer continue because of pain (8) (usually one to one and a half minutes). A sudden clattering or shrill noise was made by dropping a tin tub on the floor, or by whistling loudly. The subject was asked to solve quickly in his head the multiplication of 2 numbers of 2 digits and to have the correct answer ready when it was requested. The answer was asked in 2 minutes.

The normal subjects were young adults. In addition, there were a number of patients with various diseases (Table I), but in no case was there evidence of localized vascular disease in the parts where the measurements were made. Several patients were studied before and after preganglionic sympathectomy of the limbs. Sympathectomy of the arm was obtained by surgical division of the sympathetic trunk between the third and fourth thoracic ganglia, and section of the first and second thoracic anterior nerve roots. Sympathectomy of the leg was secured by removing the first, second, and occasionally the third lumbar ganglia.

After operation the following tests were employed to determine the completeness of the sympathectomy. 1. Measurement, by means of thermal junctions, of the temperature of the digits in a room at 20°C. 2. Measurement of reflex vasomotor activity in the digits by the technique of Bolton, *et al.* (9). 3. Detection of sweating by the technique of Minor (10) during body warming. 4. Measurement of the skin resistance by Dr. C. P. Richter (11). A forearm or calf was regarded as completely sympathectomized only when by these tests sympathetic activity was shown to be absent.

RESULTS

It was soon discovered (a) that a given stimulus did not always produce the same vasomotor effect in different subjects; (b) that in the forearm the response to a stimulus often differed from that in the calf of the same subject; and (c) that the response varied in the same limb

TABLE I

SUBJECT	AGE	SEX	WEIGHT	DIAGNOSIS	RESTING BLOOD FLOW (SUBJECT WARM), CC./100 CC./MIN.	
					Forearm	Calf
			lbs.			
W. O.	27	M	178	Normal	3.5	R 3.5 L 3.2
R. N.	28	M	180	Normal	2.3	
R. B.	18	F	112	Normal		6.5
J. D.	25	M	135	Normal	6.0	4.0
P. F.	28	M	162	Normal		3.5
R. H.	29	F		Normal	4.7	2.0
J. H.	26	M	185	Normal	6.2	3.7
A. J.	21	M	160	Normal	R 3.5 L 3.1	
W. J.	26	M	227	Normal	2.9	2.3
S. K.	39	M	130	Normal	4.6	3.0
M. K.	26	M	122	Normal	R 3.4 L 2.8	
M. P.	24	M	156	Normal	4.3	1.4
C. W.	34	M	145	Normal	R 4.8 L 3.3	
S. W.	21	F	118	Normal	4.2	2.4
P. P.	35	M		Normal	2.7	
J. S.	46	M	131	Acrocyanosis of feet	3.0	R 5.5 L 4.8 R 2.4* L 3.8*
T. J.	29	M	139	Raynaud's disease	3.5	1.9*
A. B.	33	F	140	Raynaud's disease	R 6.7 L 6.5 R 4.3* L 3.3*	6.4
R. P.	49	F	130	Raynaud's disease	R 4.3 R 2.5*	
F. G.	32	M	170	Raynaud's disease	R 4.8 L 4.5 R 3.9* L 2.8*	
F. H.	45	M	215	Raynaud's disease	R 4.0 L 4.0 L 4.7*	
C. M.	29	F	120	Raynaud's disease	R 4.0 L 4.3 R 2.4* L 2.2*	

TABLE 1—*Concluded*

SUBJECT	AGE	SEX	WEIGHT	DIAGNOSIS	RESTING BLOOD FLOW (SUBJECT WARM), CC./100 CC./MIN.	
					Forearm	Calf
			lbs.			
B. B.	33	F	114	Hypertension	6.0	R 3.5
						R 2.5*
						L 2.2*
M. C.	52	F	132	Hypertension	3.7	2.9*
E. E.	38	F	129	Hypertension	4.5	R 4.5
						L 5.0
						R 1.8*
						L 2.0*
H. F.	36	F	102	Hypertension	5.0	3.5
B. H.	21	F	123	Hypertension	3.0	2.0
S. G.	30	M	140	Hypertension	3.3	R 3.0
						L 3.6
						R 3.0*
						L 3.3*
T. R.	38	F	115	Hypertension	4.0	R 4.0
						L 4.5
					5.0	R 2.0*
						L 3.1*
C. H.	46	M	144	Hypertension	5.1	3.5
M. L.	37	M	172	Hypertension	2.5	2.0
M. N.	39	F	133	Hypertension	4.7	2.2
E. W.	50	F	101	Hypertension	1.9	1.7
M. L.	30	F	177	Hypertension	3.2	3.6
N. S.	41	F	148	Hypertension	7.3	2.4
M. W.	26	M	134	Hypertension	5.2	4.5
E. W.	38	F	140	Hypertension	5.0	4.6
B. C.	28	F	131	Microcytic anemia	4.5	2.6
S. K.	44	F	165	Microcytic anemia	5.2	3.1
F. W.	42	F	183	Pernicious anemia	4.7	3.0
W. C.	63	M	196	Acute glomerulonephritis	7.3	3.6
W. N.	14	M	98	Acute glomerulonephritis	6.5	4.1
M. B.	31	F	112	Addison's disease	3.0	2.9
C. E.	67	M	110	Addison's disease	3.7	2.1
I. H.	54	F	116	Addison's disease	3.4	3.0
E. L.	51	F	96	Addison's disease	4.0	3.0
A. T.	48	M	139	Addison's disease	3.5	2.5

* Preganglionic sympathectomy.

from time to time, even during a single experiment. No uniform cause for these variations was found. However, the response to a given stimulus was always qualitatively, and approximately quantitatively,

the same in two contralateral limbs. For this reason the response to a single stimulus in one arm could be used as a control of the response to the same stimulus in the opposite arm; and the response in the leg as a control of the opposite leg. This made it possible to determine the effect of a unilateral sympathectomy.

I. Effect of Changes in Body Warmth

Warming the body resulted in an increase in blood flow first to the forearm, and later to the calf. The time of onset of this increase varied. Sometimes it appeared in the arm after only a few minutes of warming, and before there was a detectable rise in the rectal temperature or in the temperature of the toes (Fig. 2). At other times, particularly if the subject had become thoroughly chilled by prolonged exposure in the cool room, the increase in blood flow appeared late, especially in the legs. Some increase in blood flow to the forearm was usually detectable before discomfort from overheating was reached. The increase in blood flow, whether early or late, always preceded the rise in the temperature of the skin of the opposite limb segment (Fig. 2).

During reflex vasodilatation induced by warming the body, the blood flow to both the forearm and calf was from two to four times greater than the control level obtained when the subject was cool. When reflex vasodilatation was established the blood flow to the forearms of 14 normal subjects varied from 2.3 to 7.0 cc./100 cc./min. and averaged 4.1 cc./100 cc./min., while the blood flow to the calves of 9 normal subjects varied from 1.4 to 6.5 cc./100 cc./min. and averaged 3.7 cc./100 cc./min. (Table I). Under the same conditions the blood flow to the limbs of patients with hypertension and other diseases except hyperthyroidism (13), were within the normal range (Table I).

There was no apparent explanation for the individual variations in resting blood flow. As far as could be determined, all the subjects had been brought to the same state of reflex vasodilatation. The variations could not be related to sex or weight. Since most of the subjects were in the same age group no analysis could be made of the possible influence of age. Even among subjects of the same age, sex and weight considerable individual variations in blood flow were observed. The variations could not be attributed to the shape or volume of the muscular segment enclosed within the plethysmograph,

nor to the relative proportion of skin, subcutaneous tissue, muscle, or bone as revealed by X-ray or physical examination. Differences of as much as 1.5 cc./100 cc./min. (30%) were encountered in the simultaneously measured blood flows to normal contralateral forearms.

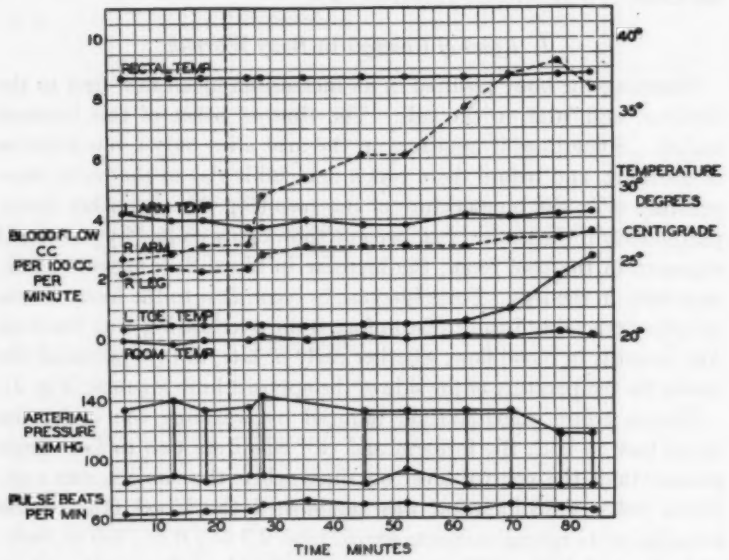

FIG. 2. *Effect of warming the body.* Chart of rectal temperature; skin temperature of the left forearm and of the left great toe; room temperature; blood flow to the right forearm, and to the right calf (interrupted lines); arterial pressure; and pulse rate during an experiment on a normal subject (S. K.). At 22½ minutes (vertical interrupted line), heating pads and blankets were placed on the subject.

In a patient who had sustained a traumatic rupture of the right brachial plexus resulting in complete denervation of the arm, the ensuing muscular atrophy had reduced markedly the size of the right arm. The volume of the segment of this forearm enclosed in the plethysmograph was 405 cc., as compared with 680 cc. for a similar segment of the contralateral normal arm. Nevertheless, the blood flow to the whole atrophic forearm segment was 17.8 cc./min. as compared with 18.4 cc./min. to the whole normal segment. When

calculated on the basis of volume, the blood flow to the atrophic forearm was actually the greater: 4.4 cc./100 cc./min. as compared with 2.7 cc./100 cc./min. for the normal arm. The atrophy seemed greatest in the muscle. It was, therefore, surprising to find that a proportionate reduction in blood flow had not occurred.

Cooling a warm subject by removing the heating pads and blankets from the body resulted in a decrease in blood flow, first to the calves, later to the forearms. In two subjects, when cooling was continued until thorough chilling (without shivering) was produced, the blood flow to the forearms was greater than during only moderate cooling. Warming the subjects then caused no further increase in blood flow, and in one, caused a slight decrease in blood flow. In this subject the "paradoxical" increase in blood flow to one forearm with excessive cooling of the body amounted to 6 cc./100 cc./min. (from 3.4 cc. to 9.3 cc./100 cc./min.).

Rôle of the Sympathetic Nervous System. In 11 patients with sympathectomized extremities, the alterations in blood flow with changes in body warmth did not occur in the sympathectomized limbs, even though they had been present before operation and still occurred in the normally innervated contralateral limb. After time for nerve-degeneration had elapsed, the blood flow with the patient warm was less after sympathectomy than before, but with the patient cool was greater than before (Fig. 3). After sympathectomy the blood flow was apparently established at a value somewhere between the low level normally produced by cooling and the higher level produced by warming. Since most people prefer to be "warm" rather than "cool", the blood flow to the forearm and calf in a "comfortable" resting state was usually reduced by sympathectomy. The occasional "paradoxical" vasodilatation with excessive cooling of the body was found in sympathectomized as well as normally innervated forearms.

II. Effect of Local Heating

When the water in the plethysmograph was raised from 32° to 40°C., the blood flow to both the forearm and calf increased. This increase in blood flow due to local heating occurred even when reflex vasodilatation from warming the body was already present (Fig. 3).

The Rôle of the Sympathetic Nervous System. An increase in blood

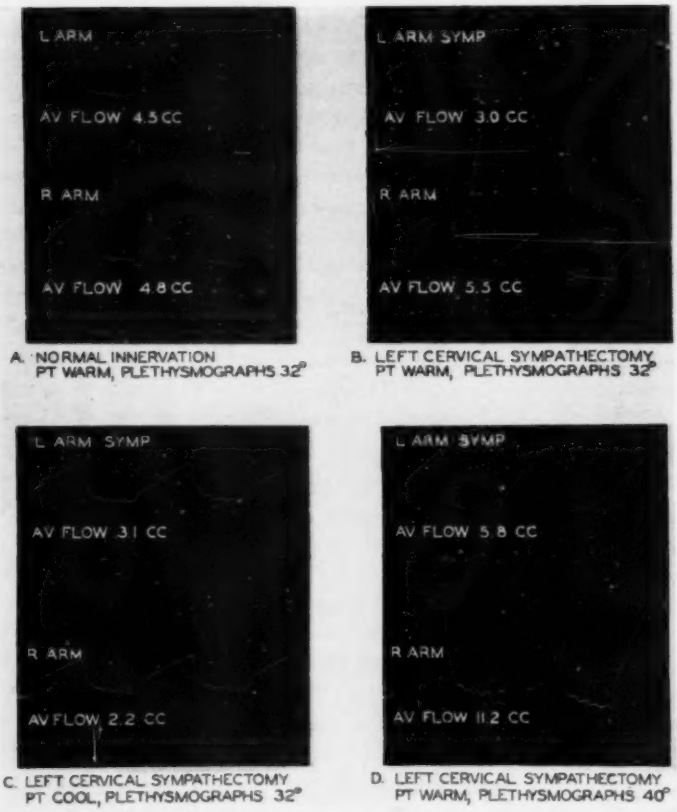

FIG. 3. Plethysmographic tracings of blood flow to the forearms of Patient F. G. with Raynaud's disease of the hands. Each set of determinations represents a different experiment. *A*, before operation; reflex vasodilatation induced by warming the body. *B*, *C* and *D*, fourteen days after left cervical preganglionic sympathectomy; reflex vasodilatation induced by warming the body and local vasodilatation induced by heating the water in the plethysmographs to 40°C. The calculated average blood flow in cc./100 cc./min. is given under each set of tracings. Time, seconds.

flow also occurred when a sympathectomized forearm or calf was heated by the water at 40°C. The resultant blood flow was not so great, however, as that to the contralateral normally innervated limb heated to the same temperature (Fig. 3).

III. Vasoconstrictor Responses

Temporary, moderate decreases in blood flow to the forearm or calf followed a number of different stimuli, such as ice applied to the skin, a pin prick in a sensitive area, the taking of a deep breath, the immersion of a hand or foot in iced or hot water, and the exercise of an ischemic arm. A decrease in blood flow with or without a significant decrease in limb volume was accepted as indicating vasoconstriction. Vasoconstriction followed the above stimuli 141 times out of the 266 times they were applied to 54 different subjects. Vasoconstriction appeared less commonly after a loud noise, and only occasionally during mental arithmetic.

The milder stimuli, which are usually effective in producing vasoconstrictions in the hands and feet, frequently were ineffective in the forearm and calf. Therefore, it was often necessary to increase the duration and intensity of a stimulus in order to obtain a vasoconstrictor response in the forearm and calf. The vasoconstrictor responses usually appeared 3 to 20 seconds after the beginning of the stimulus and persisted for varying periods of time up to a minute after cessation of the stimulus. In contralateral limbs they always appeared simultaneously, and were approximately equal, but sometimes they did not occur concomitantly in the upper and lower extremities. Responses to vasoconstrictor stimuli as a rule were less frequent and less marked in the calves than in the forearms.

The arterial pressure and pulse rate were usually not significantly affected by the milder stimuli. Marked rises in arterial pressure, and less marked increases in pulse rate, often accompanied the more severe stimuli, such as the immersion of a hand or foot in cold or hot water. However, no direct relationship existed between the degree of the vasoconstrictor response and the associated change in arterial pressure and pulse rate.

The immersion of a hand or foot in iced water was the stimulus most consistently followed by marked vasoconstriction in the forearm and calf. It caused vasoconstriction 68 times out of the 128 times it was applied to 50 different subjects. It was effective both when the subject was cool, and when the subject had been warmed and reflex vasodilatation induced. The percentage decrease in blood flow, while definite in the forearm and calf, was never so great as the decrease which occurred in the hand and foot with similar vasoconstrict-

ing stimuli. In a few subjects no significant change in blood flow occurred after this stimulus. In rare subjects increases in blood flow and limb volume appeared some 30 seconds after the beginning of the stimulus, usually following an initial vasoconstriction (see "mixed responses" below).

Rôle of the Sympathetic Nervous System. Decreases in blood flow to, and in volume of the forearm and calf after vasoconstrictor stimuli, were abolished by preganglionic sympathectomy, although vasoconstrictions still occurred in the normally innervated contralateral

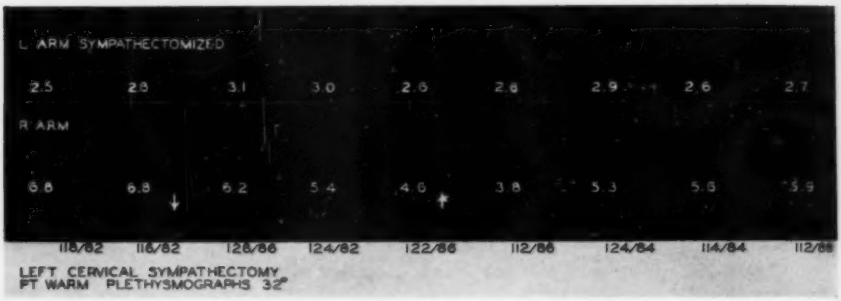

FIG. 4. Plethysmographic tracings of blood flow to the forearms of Patient C. M., who had had a left preganglionic cervical sympathectomy for Raynaud's disease of the hands. Figures under each tracing of blood flow gave its calculated value in cc./100 cc./min. Time, seconds. Signals: single, for measurement of arterial pressure, given below in mm. Hg; multiple, for start (first arrow) and finish (second arrow) of immersion of a foot in iced water.

limb (Fig. 4). In certain subjects who showed significant increases in arterial pressure during these stimuli, slight increases in blood flow occurred in the sympathectomized limbs. These slight increases were directly related to the rises of arterial pressure and were regarded as "passive".

IV. Vasodilator Responses

An increase in blood flow and limb volume often followed a loud noise, a sudden severe prick or pinch, and the request to solve mental arithmetic; and occasionally appeared after a deep breath, the application of ice to the skin, or the immersion of a hand or foot in iced

water. The nature of this response varied in different subjects; in general two different types of response were found. 1. In some subjects the increase in blood flow was only moderate, came on within 3 to 10 seconds, and passed off after the cessation of the stimulus. 2. In others there was no response until about 30 seconds after the stimulus had been applied, when the increase in blood flow appeared. It usually became marked at about 1 minute, then passed off about 2 minutes after the stimulus. In some subjects there was a combination of the two types of response, with first a moderate increase, followed by the delayed marked increase in blood flow at about 30 seconds to 1 minute after the application of the stimulus. These responses were obtained when the subject was cool and the resting blood flow low, and also when the subject had been warmed and the resting blood flow had increased as a result of reflex vasodilatation. In some subjects the aforementioned stimuli produced no effect, and in a few subjects they caused a decrease in blood flow and limb volume. Rises of arterial pressure and pulse rate often followed these stimuli, but bore no uniform relation to the changes in blood flow or limb volume. An increase in blood flow, with or without a change in limb volume, greater than the slight "passive" increase found in sympathectomized limbs during comparable rises of arterial pressure, was regarded as an indication of vasodilatation.

The mental problem was the stimulus most uniformly followed by vasodilatation: 115 times out of the 178 times it was applied to 48 subjects. It rarely produced vasoconstriction alone. However, the response was often phasic, with first an immediate slight vasodilatation, second, a slight vasoconstriction, third, a marked vasodilatation, followed, as it passed off, by a slight vasoconstriction (Fig. 5).

Vasodilator responses were best obtained when the subject was "startled" or "nervous". In one particularly emotional patient, vasodilatations of the type described above appeared "spontaneously" during the first part of an experiment. When questioned about her feelings, she replied that at those times she felt "scared". Later in the experiment she became more calm and spontaneous vasodilatations disappeared. Moreover, a "vasodilator" stimulus, after several repetitions, usually lost its effectiveness, both in producing an emotional disturbance and in causing vasodilatation in the forearm and

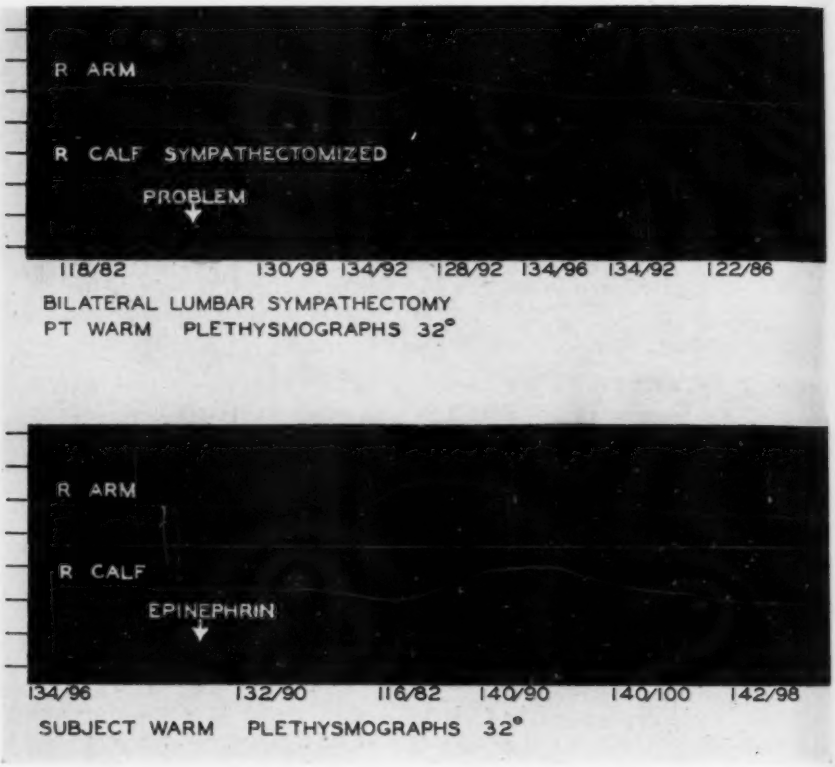

FIG. 5. Plethysmographic tracings of volume changes in the forearm and calf of Patient J. S. (upper record), and of a normal subject (lower record). The patient had had a bilateral lumbar sympathectomy for acrocyanosis of the feet. Time, seconds. Signals: single short, for measurements of arterial pressure given below in mm. Hg; multiple short, in upper record for request to solve (arrow), and request for answer to a mental arithmetical problem; single long, in lower record for intravenous injection of 1 gamma epinephrin hydrochloride. Each division of the scales appended to the left of the records equals 5 cc.

calf. Therefore, a failure of the vasodilator response to appear in a limb was not necessarily interpreted as a loss of reactivity but perhaps as an accommodation to the stimulus.

Rôle of the Sympathetic Nervous System. The immediate, moderate vasodilator response was abolished in a limb after preganglionic sympathectomy, although it still occurred in the normally innervated

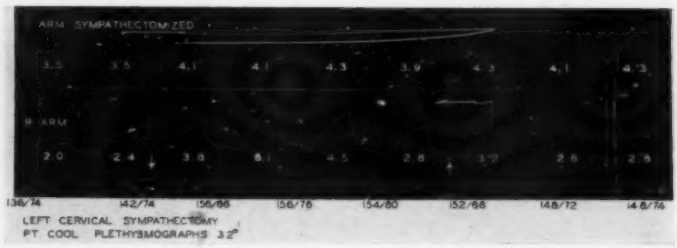

FIG. 6. Plethysmographic tracings of blood flow to the forearms of Patient F. G. who had had left cervical preganglionic sympathectomy for Raynaud's disease of the hands. Figures under each tracing of blood flow give its calculated value in cc./100 cc./min. Time, seconds. Signals: single short, for measurements of arterial pressure given below in mm. Hg; multiple (first arrow) for request to solve, and single long (second arrow) for request for answer to mental arithmetical problem.

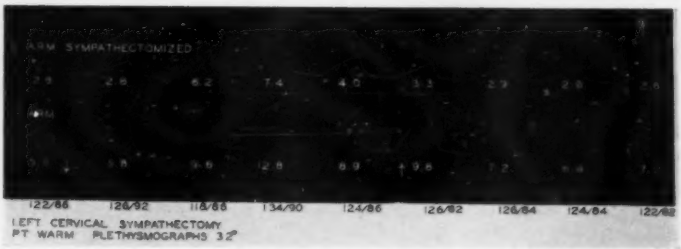

FIG. 7. Plethysmographic tracings of blood flow to the forearms of Patient C. M., who had had a left cervical preganglionic sympathectomy for Raynaud's disease of the hands. The figures under each tracing of blood flow give its calculated value in cc./100 cc./min. Time, seconds. Signals: single, for measurements of arterial pressure given below in mm. Hg; multiple, for request to solve (first arrow) and request for answer to (second arrow) a mental arithmetical problem.

contralateral limb (Fig. 6). This type of vasodilatation was, therefore, regarded as mediated over the sympathetic nervous system in the limb. The slight increases in blood flow to these sympathecto-

mized limbs which accompanied significant rises of arterial pressure were considered to be "passive".

The delayed, marked response to "vasodilator stimuli" still occurred in the completely sympathectomized forearm or calf (Figs.

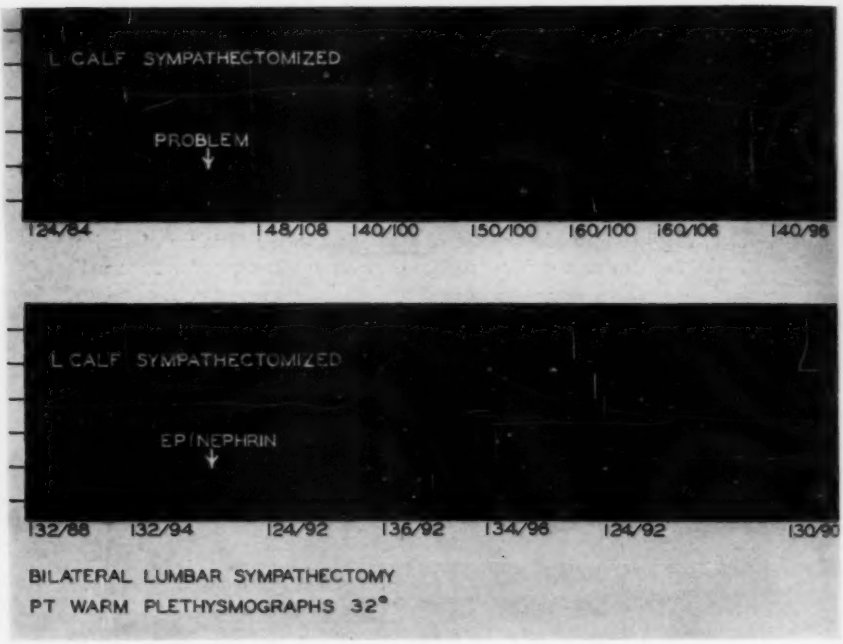

FIG. 8. Plethysmographic tracings of volume changes in the left calf of Patient J. S., who had had bilateral lumbar sympathectomy for acrocyanosis of the feet. Time, seconds. Signals: single short, for measurements of arterial pressure given below in mm. Hg. Each division of the scales appended to the left of the records equals 5 cc. At the arrow in the upper record the patient was requested to solve a mental arithmetical problem. At the arrow in the lower record 1 gamma of epinephrin hydrochloride was administered intravenously.

7 and 8). If in the normally innervated limb a combination of the immediate and delayed responses had been present, after sympathectomy the immediate vasodilatation was eliminated; but the delayed marked response persisted in its previous form, usually having three

phases: first, a slight vasoconstriction; second, a marked vasodilatation; and third, a slight vasoconstriction. This response was found also in a sympathectomized calf to which the sensory-motor nerves had been temporarily blocked by high spinal anaesthesia (Fig. 9). It was evident, therefore, that this delayed type of vasodilator response was probably "humoral" in origin.

Possible Rôle of Epinephrin. Since it is known (1, 2, 5) that the administration of epinephrin results in vasodilatation similar to the above described delayed response in the forearm and calf, 1 gamma

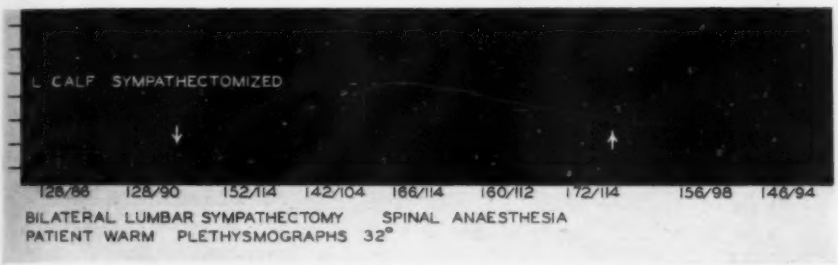
L. CALF SYMPATHECTOMIZED
128/86 128/90 152/114 142/104 166/114 160/112 172/114 156/98 146/94
BILATERAL LUMBAR SYMPATHECTOMY SPINAL ANAESTHESIA
PATIENT WARM PLETHYSMOGRAPHS 32°

FIG. 9. Plethysmographic tracing of volume changes in the left calf of Patient J. S. who had had a bilateral lumbar sympathectomy for acrocyanosis of the feet. Just before the experiment the patient had received 100 mg. of novocain crystals intrathecally at the level of the 4th lumbar vertebra. Time, seconds. Signals: single for measurements of arterial pressure given below in mm. Hg; multiple, for request to solve (first arrow) and request for answer to (second arrow) mental arithmetical problem. Each division of the scales appended to the left of the record equals 5 cc.

doses of epinephrin hydrochloride were administered intravenously to patients with sympathectomized extremities, and to normal subjects. In each group, the response to epinephrin was similar in the following ways to the delayed vasodilator response:

1. It appeared after approximately the same interval (30 to 50 seconds).

2. It appeared first in the arms, later in the legs.

3. It usually went through the same phases: a. slight vasoconstriction, b. marked vasodilatation, c. slight vasoconstriction (Fig. 5). The response to injected epinephrin was usually not accompanied by

a significant change in arterial pressure or pulse rate. Normal saline injected intravenously had no effect upon the blood flow or limb volume.

Effect of Denervation of the Adrenals. Two patients with persistent arterial hypertension who showed uniformly the delayed vasodilator response to mental arithmetic were subjected to bilateral splanchnic and lumbar sympathectomy in two stages. After the first stage, in which only one adrenal was denervated, the delayed marked vasodilator response was still present in the sympathectomized calf. However, after both adrenals had been denervated this response was never obtained in the sympathectomized calves nor in the normally innervated forearms. A moderate immediate vaosdilatation did occur in the forearms.

V. Mixed Responses

In some subjects the vasomotor responses to strong "vasoconstrictor" stimuli were mixed, showing both vasoconstriction and vasodilatation. The most frequent sequence was an initial decrease in blood flow and limb volume, succeeded about 30 to 90 seconds after the beginning of the stimulus by an increase in blood flow and limb volume. The secondary vasodilatation was usually associated with some sign of emotion. Such a response was not unusual following the immersion of the hand or foot in iced water, or after the muscular exercise of an ischemic arm.

By contrast, the vasomotor response to stimuli usually regarded as "vasodilator", occasionally consisted of an initial strong vasoconstriction, followed by vasodilatation. At other times only vasoconstriction appeared.

Such "mixed" responses were regarded as manifestations of the variability of the vasomotor reactions. A given objective stimulus does not necessarily produce the same subjective reaction in different subjects. Even in the same subject when it is prolonged over a minute, a stimulus, although objectively constant, may be subjectively changing. For example, iced water surrounding an extremity at first may be merely cold, later painful, and finally may cause a feeling of fear or anger. Mixed responses were, therefore, interpreted as combinations of the more usual, basic vasoconstrictor and vasodilator

responses. Evidence in support of this concept was obtained by the following experiment, in which strong vasoconstrictor and vasodilator procedures were simultaneously administered. A subject, who on the immersion of one hand in iced water, regularly showed a marked vasoconstriction in both the calf and the opposite forearm, was given an intravenous injection of 1 gamma of epinephrin hydrochloride as the hand was immersed in the cold water. There was an initial marked vasoconstriction merging about 1 minute later into a marked vasodilatation. The vasodilatation appeared at a time when immersion alone would have resulted in continued vasoconstriction. The vasodilatation was approximately as great as that resulting from the administration of epinephrin alone, but it appeared 30 seconds later than had been the case when epinephrin alone was used.

Rôle of the Sympathetic Nervous System. After preganglionic sympathectomy, vasomotor responses which before operation had been mixed, became modified or disappeared. The vasoconstrictions and the immediate vasodilatations were abolished, but the delayed type of vasodilatation often persisted. Furthermore, in some subjects, stimuli which had induced only vasoconstriction in the normally innervated limb, occasionally caused a delayed vasodilatation in the same limb after sympathectomy.

VI. Reactive Hyperemia

When the arterial inflow to a limb was occluded, marked increases over the control level of blood flow occurred immediately after release of the circulation. This vasodilatation quickly subsided, and the blood flow returned to the control level several minutes later. Preganglionic sympathectomy of a limb did not affect the increase in blood flow occurring during reactive hyperemia. Another communication deals in detail with blood flow to the forearm and calf during reactive hyperemia (12).

VII. Exercise

A marked increase in blood flow to the muscular segment of a limb also occurred after it was exercised. The vasodilatation from exercise persisted much longer than the vasodilatation from arterial occlusion. Preganglionic sympathectomy did not alter the vasodilatation which occurred after exercise.

VIII. Thyroid Activity

The effect of disturbed thyroid activity on the blood flow to the forearm and calf is discussed in another communication (13). It should be noted here, however, that patients with hyperthyroidism had an increased blood flow, while patients with hypothyroidism had a decreased blood flow. Treatment which brought about a change in the basal metabolic rate, also usually brought about a change in the blood flow. These changes were in the same direction but they were not necessarily proportional to each other.

DISCUSSION

As has been stated, the vasomotor reactions in the muscular segments of two contralateral limbs are normally the same. By making simultaneous measurements of blood flow, or of volume changes, in two contralateral limbs, one of which has been sympathectomized, it has been possible definitely to establish the rôle of the sympathetic nervous system in certain vasomotor reactions. Vasoconstriction on cooling the body, and vasodilatation on warming the body occur in the forearm and calf by mediation of the sympathetic nervous system. Likewise, in the forearm and calf, vasoconstrictions in response to certain stimuli, and vasodilatations in response to certain other stimuli require an intact sympathetic innervation.

The vasodilatations in response to certain "emotional" stimuli may be of two types: (a) an immediate moderate type and (b) a delayed marked type. That the immediate type of vasodilatation is mediated over the sympathetic nervous system has been demonstrated in subjects in whom unilateral preganglionic sympathectomy abolished the response only in the sympathectomized limb. That the delayed, more marked response is associated with a "humoral" factor, has been indicated by the persistence of this type of response in completely sympathectomized limbs. The striking similarity of this delayed vasodilator response to that elicited by the intravenous administration of small amounts of epinephrin hydrochloride, suggests that epinephrin may be the "humoral" factor causing the delayed type of vasodilatation after "emotional" stimuli. Evidence in support of this interpretation was obtained in two hypertensive patients who regularly manifested this type of response until after bilateral denervation of the

adrenals, when they never again showed it, either in the sympathectomized or normally innervated limbs. It is recognized that the failure to obtain the response at this time might have been due to an accommodation to the stimulus, so that it no longer had any "emotional" significance for the patient. However, both patients had shown the response in the sympathectomized limb following unilateral adrenal denervation. After the second operation they still responded to the stimulus by comparable increases in pulse rate and arterial pressure, and by nervous agitation. Moreover, the stimulus still caused an immediate moderate dilator response in the normally innervated arms. Therefore, it was thought that the stimulus probably was still adequate in "emotional" significance. A possible explanation for the absence of the delayed vasodilator response, after bilateral splanchnic and lumbar sympathectomy, is that the denervated adrenals failed to release epinephrin in sufficient quantity or at a rapid enough rate, in response to the "emotional" stimulus.

"Mixed" responses seem to be due to a combination of the vasoconstrictor and vasodilator mechanisms. The vasodilator component of certain of these mixed responses apparently also is humoral in origin, since it persists after sympathectomy. Evidence that epinephrin may be the humoral factor involved was obtained from an experiment in which a "mixed" response was "artificially" produced by immersing one hand in ice water and simultaneously injecting epinephrin.

The cause of the "paradoxical" increase in blood flow found in two subjects after excessive cooling of the body is not clear. It was found in the sympathectomized as well as the normally innervated forearms. Presumably, therefore, it was due to some humoral agent, either circulating in the blood stream, or locally concentrated in the muscular segment.

In these experiments the principal vascular tissues enclosed in the plethysmograph were skin and muscle. The site of the vasomotor reactions, whether skin or muscle, or both, could not be directly ascertained by the methods used. The increase in blood flow to the forearm and calf induced by warming the body did not seem to be, at least at first, in the superficial layers of the skin of the segment, since it appeared definitely before any rise in temperature or change in color of the skin of the opposite limb-segment. It did not require the

"superheating" which Grant and Holling (2) considered to be necessary to produce increases of skin temperature in the forearm. The vasodilatation appeared, therefore, to be in deeper structures, presumably muscle.

Local heat of 40°C. increased the blood flow in both the normal and the sympathectomized limbs. But the resultant blood flow after such local heating was definitely less in the sympathectomized limbs, which had not shown any previous reflex vasodilatation on warming the body. If one assumes that local heating dilates principally the skin vessels, it would seem that the additional reflex vasodilatation due to warming the body is probably in muscle.

Temporary reflex increases in blood flow in response to certain "emotional" vasodilator stimuli are found, so far as is known, only in limb segments containing a large proportion of muscle. In parts containing only skin and subcutaneous tissue, (e.g., the fingers) these same stimuli cause vasoconstriction. Presumably, therefore, the vasodilatation occurring in the muscular segments of limbs in response to these stimuli is in muscle. This assumption finds support from experiments on the administration of epinephrin to animals as well as to human subjects (14, 15).

In the patient who had sustained a rupture of the brachial plexus, the blood flow to the atrophic forearm was practically as great as to the normal forearm. Calculated per unit volume it was actually greater. This high blood flow in the atrophic forearm can be explained in one of two ways: 1. The blood flow in a normal forearm segment is mainly in tissues other than muscle, so that atrophy of the muscle would not significantly affect the blood flow; or 2. After denervation of an arm, the vascular tree in the muscle does not atrophy, at least at first, proportionately with the atrophy of the muscle. The second possibility seems more likely for two reasons: (a) Following the intravenous injection of 1 gamma of epinephrin hydrochloride the blood flow in the atrophic forearm segment increased as much as in the normal forearm segment; (b) During the reactive hyperemia following a five minute period of arterial occlusion the blood flow to the atrophic segment was practically as great as in the normal segment and calculated per unit volume was greater. It is known that epinephrin produces constriction of skin vessels and dilatation of muscle vessels, and that during reactive hyperemia the vessels of both

skin and muscle are dilated. It would seem, therefore, that the vessels in the atrophic forearm displayed the reactions which would be expected of muscle vessels.

The changes in blood flow and limb volume in the forearm and calf in response to vasoconstrictor stimuli were much less per unit of volume than the changes occurring in the hand or foot after similar stimuli. Furthermore, in order to obtain vasoconstrictor responses in the forearm and calf, the stimuli regularly effective in the hand and foot had to be made considerably more severe or prolonged.

The effect of sympathectomy on the resting blood flow to the forearm or calf was much less marked than the effect on blood flow to the hand and foot. When the hand or foot is sympathectomized, large increases in blood flow usually result, at least when the body is cool. But after preganglionic sympathectomy there are only small increases in blood flow to the forearm and calf with the body cool, whereas with the body warm the blood flow to the forearm and calf is actually decreased. Our observations, therefore, offer little or no rational support for the use of sympathectomy in vascular diseases associated with decreased blood flow to the forearm and calf, unless such decreases are due to a sustained vasospasm similar to that which is mediated over the sympathetic nervous system during stimulation such as the immersion of a hand or foot in iced water. Indeed, unless such vasospasm could be demonstrated, it might be argued that sympathectomy would abolish the natural *vasodilating* activity of the sympathetic nervous system in the calf and forearm. On the other hand, it is possible that after sympathectomy, vasodilatation in the hand or foot distal to the forearm or calf might enhance the development of collateral circulation to the muscular parts. Concerning this possibility we have no evidence.

SUMMARY AND CONCLUSIONS

1. In the forearm and calf reflex vasodilatation on warming the body, and reflex vasoconstriction on cooling the body are mediated by the sympathetic nervous system.

2. Transient reflex vasoconstrictions in the forearm and calf in response to certain stimuli require an intact sympathetic nervous system.

3. Vasodilatations in the forearm and calf after certain "emotional"

stimuli, are of two types: (a) the immediate, moderate vasodilatation which is reflexly mediated over the sympathetic nervous system; and, (b) the delayed, usually marked vasodilatation, which probably is humoral in origin. Evidence is given that epinephrin may be the humoral agent involved.

4. The changes in blood flow after vasoconstricting stimuli are small in the forearm and calf when compared with those which occur in the hand and foot after similar stimuli.

5. Following preganglionic sympathectomy, the blood flow to the resting forearm and calf is relatively increased when the body is cool, but is relatively decreased when the body is warm. The effects of preganglionic sympathectomy on the blood flow in the forearm and calf are small when compared with the effects in the hand and foot.

6. After preganglionic sympathectomy of a limb, some of the changes in the resting blood flow may be attributed to changes in blood pressure, but such "passive" changes in blood flow are slight.

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BIBLIOGRAPHY

1. Grant, R. T., and Pearson, R. S. B., The blood circulation in the human limb; observations on the differences between the proximal and distal parts and remarks on the regulation of body temperature. *Clin. Sc.*, 1938, **3**, 119.
2. Grant, R. T., and Holling, H. E., Further observations on the vascular responses of the human limb to body warming; evidence for sympathetic vasodilator nerves in the normal subject. *Clin. Sc.*, 1938, **3**, 273.
3. Kunkel, P., Stead, E. A., Jr., and Weiss, S., Blood flow and vasomotor reactions in the hand, forearm, foot, and calf in response to physical and chemical stimuli. *J. Clin. Invest.*, 1939, **18**, 225.
4. Abramson, D. I., and Ferris, E. B., Jr., Responses of blood vessels in the resting hand and forearm to various stimuli. *Am. Heart. J.*, 1940 **19**, 541.
5. Holling, H. E., Observations on the oxygen content of venous blood from the arm vein and on the oxygen consumption of resting human muscle. *Clin. Sc.*, 1939, **4**, 103.
6. Hewlett, A. W., and Van Zwaluwenburg, J. G., The rate of blood flow in the arm. *Heart*, 1909–10, **1**, 87.
7. Hines, E. A., and Brown, G. E., A standard test for measuring the variability of blood pressure: its significance as an index of the prehypertensive state. *Ann. Int. Med.*, 1933, **7**, 209.

8. ALAM, M., AND SMIRK, F. H., Observations in man upon a blood pressure raising reflex arising from the voluntary muscles. *J. Physiol.*, 1937, **89**, 372.
9. BOLTON, B., CARMICHAEL, E. A., AND STÜRUP, G., Vaso-constriction following deep inspiration. *J. Physiol.*, 1936, **86**, 83.
10. MINOR, V., Ein neues Verfahren zu der klinischen Untersuchung der Schweiszabsonderung. *Ber. ges. Physiol. exp. Pharm.*, 1929, **48**, 539.
11. RICHTER, C. P., AND LEVIN, M., Sympathectomy in man; its effect on the electrical resistance of the skin. *Arch. Neurol. & Psychiat.*, 1937, **38**, 756.
12. EICHNA, L. W., AND WILKINS, R. W., Blood flow to the forearm and calf. II. Reactive hyperemia: Factors influencing the blood flow during vasodilatation following ischemia. *Bull. Johns Hopkins Hosp.*, 1941, **68**, 450.
13. EICHNA, L. W., AND WILKINS, R. W., Blood flow to the forearm and calf. IV. Thyroid activity: Observations on the relation of blood flow to basal metabolic rate. *Bull. Johns Hopkins Hosp.*, 1941, **68**, 512.
14. DALE, H. H., AND RICHARDS, A. N., The vasodilator action of histamine and of some other substances. *J. Physiol.*, 1918, **52**, 110.
15. HARTMAN, F. A., EVANS, J. I., AND WALKER, H. G., The action of epinephrin upon the capillaries and fibres of skeletal muscle. *Am. J. Physiol.*, 1928, **85**, 91.
16. WILKINS, ROBERT W., AND EICHNA, L. W., Blood flow to the forearm and calf. III. The effect of changes in arterial pressure on the blood flow to limbs under controlled vasodilatation in normal and hypertensive subjects. *Bull. Johns Hopkins Hosp.*, 1941, **68**, 477.

BLOOD FLOW TO THE FOREARM AND CALF

II. Reactive Hyperemia: Factors Influencing the Blood Flow during the Vasodilatation Following Ischemia[1]

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During studies on the nature of the "peripheral resistance" of the circulation, it became desirable to produce a standard, full vasodilatation in the muscular segments of the limbs. A method was sought which would be physiologic, would require no active cooperation by the subject, would cause no discomfort and would induce no change in arterial pressure. The phenomenon of reactive hyperemia seemed well suited for this purpose. When the circulation to a limb has been arrested for a time, a marked vasodilatation occurs as soon as the circulation is released. This vasodilatation is thought to be due to the action of metabolites which accumulate locally during the period of ischemia (1).

This communication has two purposes: (a) to report certain factors which influence the blood flow to muscular segments of the forearm and calf during reactive hyperemia; (b) to describe a method, based on these studies, of obtaining a standard, full vasodilatation in the forearm and calf.

METHODS

The blood flow to muscular segments of the forearm and calf was determined by the plethysmographic method previously described (2). In order to exclude the circulation beyond the plethysmograph, the distal blood pressure cuff encircling the wrist or ankle was quickly inflated to exceed the systolic arterial pressure (250 or 300 mm. Hg). Thirty seconds later the cuff just proximal to the plethysmograph was similarly inflated. After the desired period of ischemia (2, 5, 10 or 15

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minutes) the proximal cuff was quickly deflated to a pressure of 35 to 45 mm. Hg, and the blood flow was measured during the first 5 to 15 seconds of the period of reactive hyperemia. As soon as the blood flow had been recorded, both cuffs were deflated completely. After 30 seconds the distal cuff was again inflated to 250–300 mm. Hg, and the blood flow was measured every 30 seconds throughout a recovery period which equalled the duration of the previous ischemia. Both cuffs were then deflated. Three minutes later, if desired, the procedure was repeated.

To obtain a correct plethysmographic measurement of blood flow, the pressure in the proximal cuff must be below the diastolic pressure in the local arteries. Failure to observe this point leads to obstruction of arterial inflow, and gives erroneously low values. Doupe, Newman and Wilkins (3) have shown that the local arterial pressure in a part during vasodilatation falls below the pressure measured in the larger, more central arteries. During reactive hyperemia the local arterial pressure in the muscular segment probably falls considerably below that in the central arteries where a concomitant but less extensive fall may sometimes occur. In measuring the reactive-hyperemia blood flow it was found necessary to use a pressure in the proximal cuff 30 to 40 mm. Hg below the diastolic arterial pressure as measured in the opposite brachial artery. From time to time an even lower pressure in the proximal cuff was used to make certain that arterial inflow was not obstructed.

In a blood flow determination, the plethysmographic tracing rises obliquely from the base-line and finally levels off to a plateau. The rate of inflow is represented by the ascending portion of the curve, and unless this portion rises along a straight line for at least several pulse beats, the rate of inflow cannot be accurately measured. During vasodilatation, owing to the increased blood flow and the reduced distensibility of the vascular bed, the ascending portion of the curve is sometimes of inadequate length, lasting for only one or two pulse beats. When these conditions were encountered the following alternate procedure was employed: Thirty seconds after the inflation of the distal cuff, ischemia of the segment was begun by introducing *into the plethysmograph* a pressure of 250 to 300 mm. Hg. This maneuver squeezed blood out of the muscular segment. After 30 seconds the proximal cuff was inflated to the same pressure as that within the plethysmograph. A few seconds later the pressure in the plethysmograph was reduced to atmospheric, and after the desired period of ischemia the blood flow was measured in the manner previously described. This alternate procedure was designed to provide a larger reservoir for the incoming blood. As a result, the straight obliquely ascending portion of the inflow tracing was increased to the length required for accurate measurements. Earlier experiments, upon suitable subjects, had shown that the angle of ascent of the tracing was not altered by the preliminary expression of blood from the muscular segment.

The general conditions of the experiments have been stated in a previous paper (2). The subject lay supine in bed with the head elevated 5° to 10°. Except as

otherwise noted, general reflex vasodilatation was induced by warming the body until the skin temperature of both the fingers and the toes had reached 33° to 35°C. The limb segment enclosed in the plethysmograph was at heart level. The temperature of the water in the plethysmograph was 32°C., unless purposely changed. Room temperature was usually 20°C. The arterial pressure was determined during each measurement of blood flow. All sympathectomies were of the preganglionic type and the criteria of their completeness were those noted in a previous study (2).

RESULTS

This communication is concerned solely with the blood flow to the forearm and calf during the first 5 to 15 seconds of reactive hyperemia. Unless otherwise specifically qualified, the term *reactive-hyperemia blood flow*, or, simply blood flow, will refer to the measurements so obtained. The reactive-hyperemia blood flow is much greater than the blood flow as ordinarily measured in the resting limb (to be called, hereafter, *resting blood flow*).

Variations in the Plethysmographic Tracing. The first portion of the tracing was often distorted. The initial inflation of the proximal cuff to 250 or 300 mm. Hg usually caused displacement of soft tissue into the plethysmograph. Deflation of the cuff to the lower "collecting" pressure at the beginning of the blood flow determination permitted a return of the tissue to a more normal position. The resultant drop in the base line distorted the upward sweep of the tracing for 1 to 2 seconds. This distortion could be avoided by moving the proximal cuff away from the plethysmograph. But this introduced a greater error by permitting blood to collect between the proximal cuff and the plethysmograph, where it could not be measured. Therefore, the proximal cuff was kept as close as possible to the plethysmograph and the initial, distorted portion of the tracing was rejected as an artefact. Beyond this artefact, the ascending line usually manifested a short, gradual, initial slope merging into a longer and steeper, straight main portion. Calculations of blood flow were always made from the longer, steeper, straight portion of the tracing.

Collecting Pressure. Provided it was below the local diastolic pressure, the collecting pressure in the proximal cuff during reactive hyperemia usually could be varied widely without materially affecting the blood flow. But in some instances, the higher the collecting pressure (up to 55 mm. Hg) the greater the calculated blood flow.

Often this seemed to be due to a greater distention of the part during the higher collecting pressure, giving a longer and steeper line. On the other hand, when the collecting pressure was too low (20 to 30 mm. Hg) little distention of the part occurred, and the resultant tracing quickly flattened to its plateau. The variations caused by changes in the collecting pressure were usually more marked in the blood flow to the forearm than in that to the calf. Occasionally, varying the collecting pressure altered the calculated blood flow by as much as 5 cc. to 6 cc./100 cc./min. Usually the difference did not exceed 2 cc. to 3 cc./100 cc./min. To avoid these possible variations, determinations were always made at the same collecting pressure when measuring the blood flow in the same individual from time to time, or when comparing the flow in one subject with that in another.

Augmentation of Successive Blood Flows. A characteristic feature of the reactive-hyperemia blood flow was its augmentation with successive determinations. Under strictly controlled conditions, the second blood flow generally exceeded the first, and the third was usually greater than the second. However, by about the fourth determination the blood flow reached a maximum and thereafter little or no further increase occurred with successive determinations (Figs. 1 and 2). This phenomenon failed to appear in the blood flow to the forearm of only 2 of 48 subjects, and to the calf of only 4 of 42 subjects. In the normal group, the augmentation of blood flow from the first to the fourth determination varied in the forearm from 1 cc. to 9 cc./100 cc./min. (average 5.5 cc./100 cc./min.), and in the calf from 1 cc. to 8 cc./100 cc./min. (average 4.0 cc./100 cc./min.). The increase usually was 20 per cent to 25 per cent of the initial blood flow and was never more than 30 per cent.

Augmentation of blood flow with successive determinations occurred whether the blood in the limb-segment was or was not expelled during the first half minute of the ischemic period. It occurred regardless of the duration (5 or 15 minutes) of the ischemic period preceding the first of a series of blood flow determinations. The state of peripheral reflex vasodilatation did not affect it, for it occurred as readily in subjects who were cold and had low skin temperatures, as in those in whom full reflex vasodilatation had been induced by warming the body. It was encountered in sympathectomized forearms and calves as

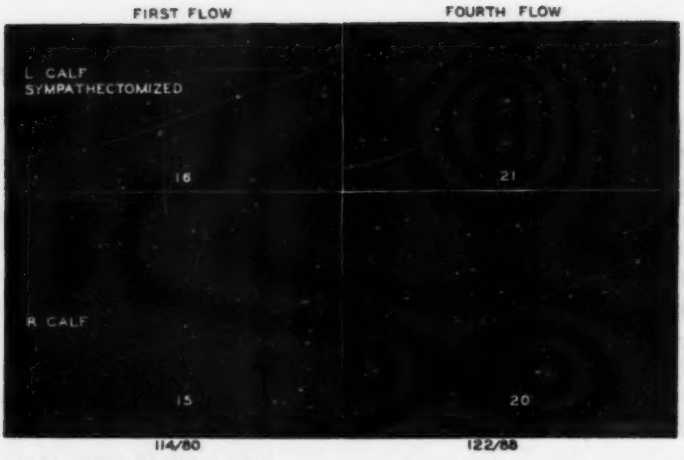

FIG. 1. Plethysmographic tracings of reactive-hyperemia blood flow to both calves of a patient (J. S.) who had had a left lumbar sympathectomy for acrocyanosis of the feet. The calculated blood flow, in cc./100 cc./min., is given under each tracing. Time, seconds (and quarter-seconds). Arterial pressure in mm. Hg is given below. The tracings on the left were the first in a series of determinations; those on the right, the fourth in the series.

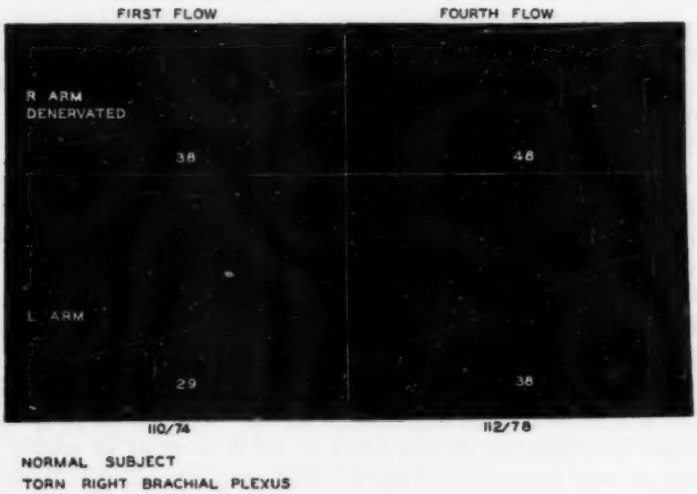

FIG. 2. Plethysmographic tracings of reactive-hyperemia blood flow to both forearms of a patient (P. P.) who had sustained a torn right brachial plexus. The tracings on the left were the first in a series of determinations; those on the right, the fourth in the series. (For further explanation see legend of Fig. 1.)

well as in normally innervated extremities (Fig. 1). It was observed in the atrophic, completely denervated forearm of a patient who had sustained a traumatic severance of the brachial plexus (Fig. 2).

Further evidence that this phenomenon is determined by local factors, was obtained in the following experiment. With the circulation to the contralateral extremity undisturbed, three to four successive reactive-hyperemia blood flow determinations were made on one extremity alone. When the blood flow values for this extremity had reached their maximum level, successive blood flow determinations were continued on both extremities simultaneously. The blood flow to the second limb showed the usual increase with successive determinations, while that to the first extremity remained at its established maximum value.

All further statements concerning blood flow during reactive hyperemia refer to values obtained after full augmentation with successive determinations had occurred.

Duration of the Preceding Ischemia. Provided no change in arterial pressure was induced, the blood flow was but little increased by prolonging the ischemic period beyond 5 minutes. After the customary augmentation of successive flows had occurred, the blood flow following 10 or 15 minutes of ischemia sometimes exceeded that following a 5-minute period of ischemia, but rarely by more than 5 cc./100 cc./min. (20 per cent) (Table I). The longer periods of ischemia often induced paresthesias or pain, and were then accompanied by rises in arterial pressure to which the increases in blood flow were probably attributable. Occasionally the blood flow following the longer periods of circulatory arrest was less than that following five minutes of ischemia. Prolongation of the ischemia did lengthen the time required for the return of the blood flow to its initial resting level. These relationships between the duration of ischemia and the blood flow were the same in sympathectomized limbs as in normally innervated limbs.

A five-minute period of circulatory arrest proved to be the most satisfactory for it caused no discomfort and no rise in arterial pressure; it was, therefore, employed as a standard vasodilating stimulus. All further observations on blood flow during reactive hyperemia were made after occluding the circulation for a five-minute period.

Reflex Vasodilatation and Local Heat. Little or no increase in re-

TABLE I

Effect of Duration of Ischemia on Subsequent Reactive-Hyperemia Blood Flow

SUBJECT (SEX, AGE)	WEIGHT	DIAGNOSIS	FIVE MINUTES ISCHEMIA			TEN MINUTES ISCHEMIA			FIFTEEN MINUTES ISCHEMIA			REMARKS
			Blood Flow, cc./100 cc./min.		Arterial Pressure	Change in Blood Flow, cc./100 cc./min.		Change in Arterial Pressure	Change in Blood Flow cc./100 cc./min.		Change in Arterial Pressure	
			Forearm	Calf		Forearm	Calf		Forearm	Calf		
	lbs.				*mm. Hg*			*mm. Hg*			*mm. Hg*	
J. H. (M, 28)	185	Normal	R 37	R 24	120/76				+5	+1	+6/ +4	
R. N. (M, 26)	180	Normal	31		124/76	−4		+2/ +6				
W. O. (M, 26)	178	Normal	28		134/84	−5		−6/ −4				
				R 27	134/86		+1	0/ 0				
				L 25	134/86		+1	0/ 0				
			R 30	R 25	120/80				+3	+3	+6/ 0	
M. P. (M, 24)	156	Normal	R 33	R 38	122/84				+3	+2	+4/ +2	
				L 37	118/80		−6	0/ −2		−3	+6/ +2	
P. P. (M, 35)		Normal (severance rt. brachial plexus)	R 48*		112/78	−4*		0/ −2				Right arm completely denervated and atrophic
			L 38		112/78	−4		0/ −2				
P. F. (M, 28)	162	Normal		L 30	116/74		0	−2/ +2		0	−2/ +2	
C. S. (M, 45)	126	Hyperthyroid (treated)	R 38	R 22	122/70				−1	+1	−4/ +2	BMR +3%
			R 28	R 17	118/86				−6	+1	+10/ 0	BMR −24%
H. J. (M, 47)	130	Hyperthyroid	R 34	R 30	152/102	+13	+10	+34/+24				BMR +80%
			R 40	R 29	152/112	+11	+2	+6/ 0				BMR +17% (treated)
L. M. (F, 45)	150	Hyperthyroid	R 45	R 28	190/108	0	+2	−2/ −6				BMR +64%
			R 44	R 27	184/92	+14	+5	+4/+10				BMR +44% (treated)

D. H. (F, 19)	126	Hyperthyroid	R 49 R 55 R 36	R 26 R 25 R 18	138/58 144/64 116/72	+10 +10 −2	+4 +9 +1	+10/+16 +18/+10 −4/ +2				BMR +71% BMR +77% BMR −5% (treated)
J. F. (M, 21)	144	Hyperthyroid	R 36 R 41	R 32 R 31	134/80 126/80	+14 +2	+8 +3	+12/ +2 0/+10				BMR +32% BMR −4% (treated)
F. G. (M, 32)	170	Raynaud's disease	L 23 R 30 L 23* R 29*		138/80 138/80 132/82 132/82				+1 +3 +1* +1*		+6/ +2 +6/ +2 +2/ +2 +2/ +2	Sympathectomized
R. B. (M, 47)	181	Postural hypotension		R 24	94/62		+2	+4/ 0				
E. L. (F, 51)	96	Addison's disease	R 26 R 30	R 14 R 19	112/78 120/82				−1 +4	+2 +3	−2/ −2 +6/ +4	Before treatment After treatment
B. C. (F, 28)	131	Anemia (microcytic hypochromic)	R 37 R 33 R 37	R 22 R 18 R 24	104/62 106/80 104/76				−3 −2 +1	0 +3 +4	−2/ +2 0/ −4 +10/ +6	Hgb. 6.4 gm. Pt. dehydrated. Hgb. same Hgb. 12.6 gm.
S. K. (F, 44)	165	Anemia	R 51 R 35	R 25 R 24	182/120 210/136				+4	+5 +2	+20/ +2 +2/ −2	Hgb. 7.0 gm. Hgb. 12.5 gm.
M. C. (F, 52)	132	Hypertension	R 34	L 18* L 22*	146/106 146/104	+6	+3* +1*	+20/ +8 −2/ +1				Bilateral splanchnic and lumbar sympathectomy
M. L. (F, 30)	176	Hypertension	R 32	R 26	146/110				0	+2	−2/ −4	
E. W. (F, 50)	101	Hypertension	R 32	R 23	182/120	+3	+4	+16/+18				
. N. (F, 39)	133	Hypertension	R 40	R 25	172/116				+8	+4	+12/+20	

R = right limb; L = left limb.
* Sympathectomized limb.

TABLE I—*Concluded*

SUBJECT (SEX, AGE)	WEIGHT	DIAGNOSIS	FIVE MINUTES ISCHEMIA			TEN MINUTES ISCHEMIA			FIFTEEN MINUTES ISCHEMIA			REMARKS
			Blood Flow, cc./100 cc./min.		Arterial Pressure	Change in Blood Flow, cc./100 cc./min.		Change in Arterial Pressure	Change in Blood Flow, cc./100 cc./min.		Change in Arterial Pressure	
			Forearm	Calf		Forearm	Calf		Forearm	Calf		
	lbs.				*mm. Hg*			*mm. Hg*			*mm. Hg*	
M. L. (M, 37)	172	Hypertension	R 31	L 22*	184/124	+2	0*	−10/ −8				Left splanchnic and lumbar sympathectomy
C. H. (M, 46)	144	Hypertension	R 50	R 34	196/142				+8	+8	+10/ 0	
T. R. (F, 38)	115	Hypertension	R 39		166/116	−1		−4/ 0				Rt. sympathectomy bilateral splanchnic and lumbar sympathectomy
				R 33	162/120		+2	+4/ +4				
				R 24	164/116		+2	−6/−10				
			R 39	R 29*	174/126	+2	−3*	−6/ −4				
				L 27*	160/114		L 0*	0/ −6				
				R 24*			R +1*					
			R 32	R 26*	164/116	0	−2*	0/ −2				
S. G. (M, 30)	140	Hypertension	R 47	R 37*	218/176	0	+1*	+4/ −2				Bilateral splanchnic and lumbar sympathectomy
B. H. (F, 21)	123	Hypertension	L 59		208/142	+4		−12/ −6				
				L 39	204/146		−2	−16/ −8				
			L 56		192/136	−5		+4/ −8	+3		−14/−10	
H. F. (F, 36)	102	Hypertension	L 47		228/150	−8		−6/ −4				
			L 30	L 30	244/178	+2	+3	−10/ −6				
E. E. (F, 38)	129	Hypertension	R 40	R 21*	118/102	−1	−2*	−6/ −8				Arterial pressure lowered by previous bilateral splanchnic and lumbar sympathectomy
			R 42	L 25*	122/98	+1	−1*	0/ +4				

active-hyperemia blood flow resulted from the induction of full reflex vasodilatation (Table II). The maximum recorded increase of 25 per cent contrasts markedly with the 100 per cent to 300 per cent

TABLE II

Effect of Reflex Vasodilatation on Reactive-Hyperemia Blood Flow

SUBJECT	DIAGNOSIS	COOL			REFLEXLY VASODILATED		
		Blood Flow, cc./100 cc./min.		Arterial Pressure	Blood Flow, cc./100 cc./min.		Arterial Pressure
		Forearm	Calf		Forearm	Calf	
				mm. Hg			mm. Hg
S. K. (M, 39)	Normal	L 28	L 22	140/88	L 35	24	140/90
J. S. (M, 46)	Acrocyanosis of feet	R 28	R 20	132/84	35	16	124/90
		R 30	L 20*	124/88	24	19*	118/92
			L 21	126/88		18	118/82
			R 19	126/88		16	118/82
			L 16*	124/86		13*	122/100
			R 12	124/86		11	122/100
			L 20*	124/84		19*	134/92
			R 19	124/84		17	134/92
F. G. (M, 32)	Raynaud's disease	L 26		146/80	26		144/78
		R 31		146/80	32		144/78
		L 22*		134/70	22*		136/78
		R 26		134/70	28		136/78
F. H. (M, 38)	Raynaud's disease	L 30		132/96	24		?
		R 26		132/96	24		?
C. M. (F, 29)	Raynaud's disease	L 27		118/76	28		120/74
		R 28		118/76	29		120/74
C. H. (M, 46)	Hypertension	R 44	R 22	176/128	37	20	176/128

L = left limb; R = right limb.
* Sympathectomized limb.

increases in the *resting* blood flow, which occur regularly when the body is warmed (2).

When reflex vasodilatation had been induced by warming the subject, raising the temperature of the water in the plethysmograph from 32° to 40°C. usually caused a further small increase in the reactive-

hyperemia blood flow (Table III). The greatest recorded increase (15 per cent) was much less than the increases in the *resting* blood flow which occur when the local temperature is similarly raised (2).

The reactive-hyperemia blood flow to the sympathectomized forearm and calf was unaffected by reflex vasodilatation, but was affected by local heating in the same manner as the blood flow to the normally innervated limb.

TABLE III

Effect of Local Temperature on Reactive-Hyperemia Blood Flow

SUBJECT	DIAGNOSIS	PLETHYSMOGRAPH TEMPERATURE 32°C.			PLETHYSMOGRAPH TEMPERATURE 40°C.		
		Blood Flow, cc./100 cc./min.		Arterial Pressure	Blood Flow, cc./100 cc./min.		Arterial Pressure
		Forearm	Calf		Forearm	Calf	
				mm. Hg			*mm. Hg*
F. G. (M, 32)	Raynaud's disease	L 26		144/78	27		142/82
		R 32		144/78	35		142/82
		L 22*		136/78	20*		134/84
		R 28		136/78	28		134/84
F. H. (M, 38)	Raynaud's disease	L 30*		106/68	30*		116/74
C. M. (F, 29)	Raynaud's disease	L 27*		118/72	29*		116/76
J. S. (M, 46)	Acrocyanosis of feet		L 22*	126/90		23*	146/102
			R 20	126/90		22	146/102
			L 21*	122/88		23*	132/96
			R 20	122/88		23	132/96

L = left limb; R = right limb.
* Sympathectomized limb.

Vasoconstrictor Stimuli. Vasoconstrictor stimuli were applied during, or immediately preceding the determination of the reactive-hyperemia blood flow. The milder stimuli, of short duration, producing no elevation of the arterial pressure, caused little or no change in the blood flow (1 to 2 cc./100 cc./min.). Among these stimuli were deep breathing, the application of ice to the neck or face, and pricking the skin. Similar stimuli often reduce considerably the *resting* blood flow (2).

Unpredictable changes in the reactive-hyperemia blood flow were associated with the more severe vasoconstricting stimuli, such as the immersion of an extremity in iced water (4), which often caused considerable discomfort and usually a rise in arterial pressure. When compared with the control values, the blood flows obtained during this "cold test", fell into three groups (Table IV): (a) Those that showed no significant change. This group was numerically the smallest. (b) Those that showed a decrease, sometimes to a marked degree, even in association with a substantial rise in arterial pressure (Fig. 3).

TABLE IV

Changes Induced in the Reactive-Hyperemia Blood Flow during the Cold Test

TYPE OF SUBJECT	NUMBER OF SUBJECTS IN WHOM BLOOD FLOW TO LIMBS WAS DETERMINED		NUMBER OF SUBJECTS SHOWING AN INCREASE IN BLOOD FLOW TO		NUMBER OF SUBJECTS SHOWING A DECREASE IN BLOOD FLOW TO		NUMBER OF SUBJECTS SHOWING NO CHANGE IN BLOOD FLOW TO		TOTAL NUMBER OF SUBJECTS TESTED
	Forearm	Calf	Forearm	Calf	Forearm	Calf	Forearm	Calf	
Normal	6	5	5	4			1	1	8
Hyperthyroid	1	1	1	1					1
Vascular disease, hands or feet	2	2	2	2					4
Addison's disease	3	3	2	2	1	1			3
Anemia	2	2	2	2					2
Hypertension	13	11	8	5	3	4	2	2	14
Acute nephritis	2	2		1	2			1	2
Totals	29	26	20	17	6	5	3	4	34

A significant change differs from the control value by more than 2 cc./100 cc./min.

This group was also small. (c) Those that showed an increase, of a variable degree (Fig. 4). This group comprised about two-thirds of all subjects. In these subjects there was almost invariably a substantial increase in the arterial pressure associated with the increase in blood flow. During the cold stimulation, the alteration in the blood flow to normally innervated limbs apparently resulted from the action of two opposing and variably effective factors: (a) a rise in arterial pressure tending to increase the flow, and (b) a local vasoconstriction operating to decrease the flow.

The effect produced by vasoconstrictor stimuli varied not only from subject to subject, but sometimes even from day to day in the same

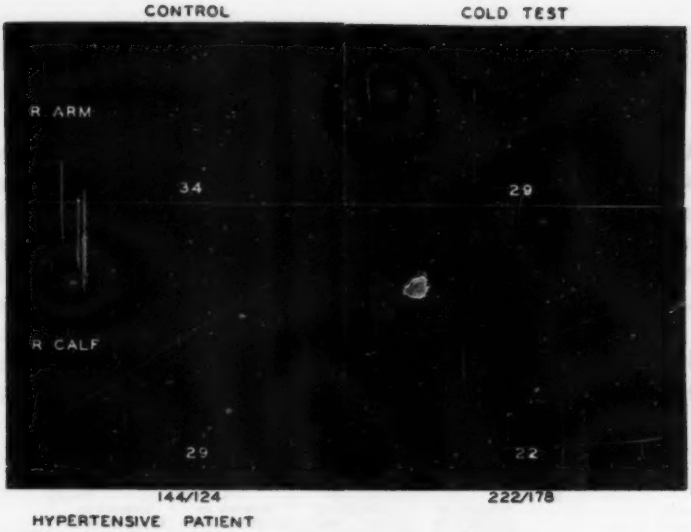

FIG. 3. Plethysmographic tracings of reactive-hyperemia blood flow to the right forearm and calf of a hypertensive patient (E. W.). The tracings on the left were obtained during the control period, those on the right during the immersion of a hand in iced water. (For further explanations see legend of Fig. 1.)

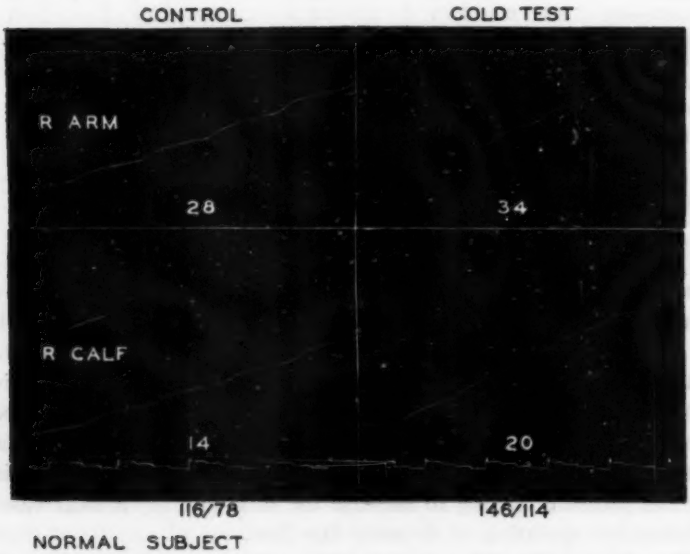

FIG. 4. Plethysmographic tracings of reactive-hyperemia blood flow to the right forearm and calf of a normal subject (R. H.). The tracings on the left were obtained during the control period, those on the right during the immersion of a hand in iced water. (For further explanations see legend of Fig. 1.)

limb. As a rule, similar qualitative changes in blood flow occurred in contralateral extremities, but the quantitative effects on the two sides, though approximately the same, were not always identical.

Sympathetic Nervous System. In a number of subjects, the reactive-hyperemia blood flow to an extremity was determined both before

TABLE V

Effect of Preganglionic Sympathectomy on Reactive-Hyperemia Blood Flow

SUBJECT	DIAGNOSIS	BEFORE SYMPATHECTOMY			AFTER SYMPATHECTOMY		
		Blood Flow, cc./100 cc./min.		Arterial Pressure	Blood Flow, cc./100 cc./min.		Arterial Pressure
		Left	Right		Left	Right	
Forearms							
				mm. Hg			*mm. Hg*
B. B. (F, 44)	Scleroderma	25–26	28	114/88	18	22–29	114/90
F. G. (M, 32)	Raynaud's disease	23–26	30–31	142/80	22–24	29	134/84
F. H. (M, 38)	Raynaud's disease	30	26	132/96	30		106/68
C. M. (F, 29)	Raynaud's disease	27	28	118/76	27	27	116/76
R. P. (F, 49)	Raynaud's disease		28	136/96		24	116/86
Calves							
J. S. (M, 46)	Acrocyanosis of feet	21	19–20	128/86	18–26	22	120/86
B. B. (F, 33)	Hypertension	14	18–24	168/116	17	17	156/118
E. E. (F, 38)	Hypertension	27	32	178/136		31	182/146
					19–25	20–31	120/100
S. G. (M, 30)	Hypertension	38–40	38–40	202/150	35–42	37	220/174
T. R. (F, 38)	Hypertension	25		212/146		24	200/146
			24–33	162/118	23–27	22–29	168/124

and after preganglionic sympathectomy. When sufficient time had elapsed for nerve-degeneration, the reactive-hyperemia blood flow was usually about the same as it had been before operation (Table V). However, in two of six subjects, unilateral sympathectomy was associated with an immediate decrease (4 cc. and 8 cc./100 cc./min., respectively) in the reactive-hyperemia blood flow to the contralateral, normally innervated limb. In one of these subjects a decrease

of 5 cc./100 cc./min. also occurred in the sympathectomized member. All these immediate reductions were temporary, the reactive-hyper-

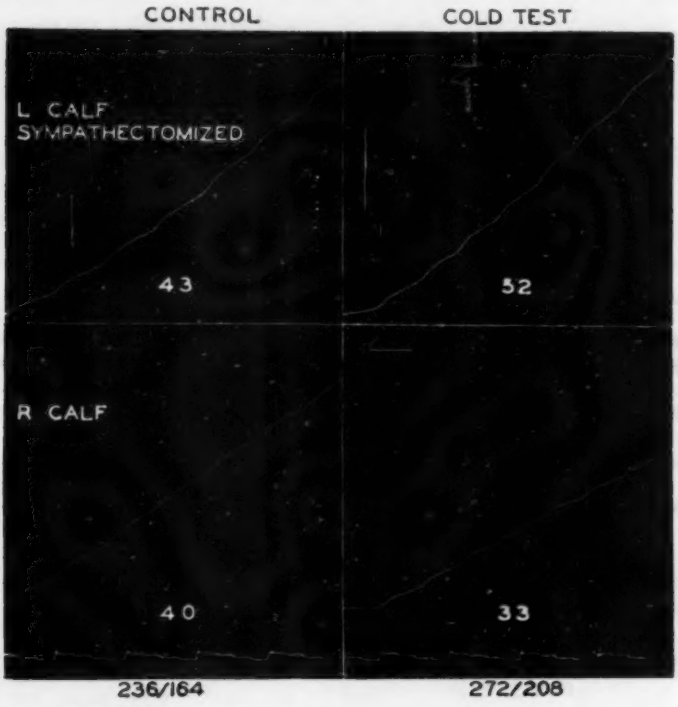

FIG. 5. Plethysmographic tracings of reactive-hyperemia blood flow to both calves of a hypertensive patient (S. G.) who had had a left splanchnic and lumbar sympathectomy. The tracings on the left were obtained during the control period, those on the right during the immersion of a hand in iced water. (For further explanations see legend of Fig. 1.)

emia blood flow returning within several days to its preoperative level and remaining there.

During strong vasomotor stimuli, sympathetic nervous system

activity may cause substantial alterations in the reactive-hyperemia blood flow. For example, in the patient whose blood flows are illustrated in Figure 5, the cold test induced a marked rise in arterial pressure and with it a considerable increase in blood flow to the sympathectomized left calf, but the simultaneously determined blood flow to the contralateral, normally innervated calf decreased sharply.

During vasoconstrictor stimuli the reactive-hyperemia blood flow to sympathectomized limbs always varied directly and generally proportionately with the arterial pressure. A previous study showed

TABLE VI

Changes Induced in the Reactive-Hyperemia Blood Flow during Mental Arithmetic

TYPE OF SUBJECT	NUMBER OF SUBJECTS IN WHOM BLOOD FLOW TO LIMBS WAS DETERMINED		NUMBER OF SUBJECTS SHOWING AN INCREASE IN BLOOD FLOW TO		NUMBER OF SUBJECTS SHOWING A DECREASE IN BLOOD FLOW TO		NUMBER OF SUBJECTS SHOWING NO CHANGE IN BLOOD FLOW TO		TOTAL NUMBER OF SUBJECTS TESTED
	Forearm	Calf	Forearm	Calf	Forearm	Calf	Forearm	Calf	
Normal	4	4	3	3			1	1	5
Hyperthyroid	1	1	1	1					1
Vascular disease, hands or feet	2		2						2
Addison's disease	1	1	1	1					1
Anemia	1	1	1					1	1
Nephritis	1	1	1			1			1
Hypertension	13	11	4	3	4		5	8	13
Totals	23	19	13	8	4	1	6	10	24

A significant change differs from the control value by more than 2 cc./100 cc./min.

that preganglionic sympathectomy of a limb abolishes the local vasoconstrictor responses to such stimuli (2). The reactive-hyperemia blood flow to sympathectomized limbs presumably, therefore, was a function chiefly of one variable, the arterial pressure. The relationship of the blood flow and arterial pressure is discussed in detail in another communication (5).

"Vasodilator" Stimuli. Table VI shows the changes induced in the reactive-hyperemia blood flow during the vasodilatation produced by solving an arithmetical problem (2, 6). Even in normally innervated limbs these changes usually varied directly, but not always propor-

tionately, with the simultaneous changes in arterial pressure. Rarely, no increase, or even a decrease, in blood flow accompanied a rise in arterial pressure. In sympathectomized extremities the blood flow during mental arithmetic varied directly and proportionately with the change in arterial pressure.

Minute amounts (1 to 2 gamma) of intravenously injected epinephrin, without altering the arterial pressure, induce vasodilatation in the normally innervated and sympathectomized resting forearm and calf (2, 7). In a subject with a sympathectomized calf, when one gamma of epinephrin hydrochloride was injected, the reactive-hyperemia blood flow, at the peak of the resulting vasodilatation, was the same as it had been before the injection.

Local, Ischemic, Muscular Exercise. The forearm muscles in the plethysmograph were exercised by having the subject squeeze a blood pressure bulb once a second for one minute. The exercise was begun 3½ minutes after the start of a 5 minute period of ischemia and was continued until ½ minute before release of the circulation and measurement of blood flow. This procedure always induced a rise in arterial pressure (Alam and Smirk (8)), associated with which there was usually an increase in the reactive-hyperemia blood flow. The increase in blood flow was attributed mainly to the rise in arterial pressure rather than to local factors, for it was demonstrated in two subjects that approximately the same rises in arterial pressure and increases in blood flow occurred regardless of whether the ischemic exercise were performed by the arm in the plethysmograph or by the opposite arm.

Sleep, Natural and Induced. During measurements of blood flow, subjects often fell asleep. At such times the reactive-hyperemia blood flow was not altered from that obtained in the waking state. In five subjects a deep sleep was induced by the oral administration of 0.2 gram of sodium amytal every hour for 3 doses (9). When narcosis induced by sodium amytal was not associated with a change in arterial pressure, the blood flow remained unaltered; but when the arterial pressure fell, the blood flow decreased correspondingly.

Thyroid Activity and Basal Metabolic Rate. Another communication (10) will report in greater detail observations on the effect of thyroid activity and the basal metabolic rate upon the blood flow

to the forearm and calf. In hyperthyroid patients the reactive-hyperemia blood flow tended to be greater than in normal subjects, while in hypothyroid patients it tended to be less than in normal subjects.

Arterial Pressure. Of all the factors which were found to influence the reactive-hyperemia blood flow, the arterial pressure was the one which exerted the most consistent and profound effects. A subsequent communication (5) deals with this factor in detail and points out that, under certain conditions, a direct linear relationship exists between blood flow and arterial pressure.

Variation in Blood Flow to the Same Limb. Under standard conditions, and with all of the aforementioned modifying factors controlled, variations still occurred from time to time in the measurements of reactive-hyperemia blood flow to the same limb (Table VII). In general, the larger variations were encountered when the determinations were made at intervals of several months to a year. When the determinations were made on successive days or at intervals of several days to a few weeks, the variations rarely exceeded 3 cc./100 cc./min.

The maximum differences between the reactive-hyperemia blood flows measured on different days in the same extremity, were as follows:

Normal forearm, 6 subjects, 0 cc. to 6 cc./100 cc./min. (0 to 20 per cent).

Normal calf, 3 subjects, 2 cc. to 3 cc./100 cc./min. (8 to 15 per cent).

Forearm, 8 hypertensive subjects, 1 cc. to 11 cc./100 cc./min. (3 to 26 per cent).

Calf, 8 hypertensive subjects, 0 cc. to 11 cc./100 cc./min. (0 to 39 per cent).

In one hypertensive patient a difference of 20 cc./100 cc./min. (54 per cent) was found between two determinations made six months apart. In occasional subjects, shortly after surgical procedures, temporary differences were encountered, which were as great as 30 per cent in the forearm and 44 per cent in the calf.

The blood flow to the same sympathectomized limb also varied moderately from day to day:

In three sympathectomized forearms of two subjects the greatest variation was 4 cc./100 cc./min. (15 per cent). In a patient who had had a bilateral lumbar ganglionectomy for acrocyanosis of the feet, the blood flow to the sympathectomized left calf was determined on eleven different occasions. On eight of these occasions it was always between 18 cc. and 22 cc./100 cc./min., but on one day (shortly after operation) it was as low as 16 cc./100 cc./min. and on another as high as 26 cc./100 cc./min. In six sympathectomized calves of four hypertensive

TABLE VII

Variations in Reactive-Hyperemia Blood Flow to the Same Limb on Different Days

SUBJECT (SEX, AGE WEIGHT)	DIAGNOSIS	FOREARMS				CALVES			
		Date	Blood Flow, cc./100 cc./min.		Arterial Pressure	Date	Blood Flow, cc./100 cc./min.		Arterial Pressure
			Left	Right			Left	Right	
					mm. *Hg.*				mm. *Hg.*
S. K. (M, 39) 130 lbs.	Normal	1/20/40	31	33	140/88				
		1/23/40		39	138/94				
		1/25/40	28		140/88				
W. O. (M, 26) 178 lbs.	Normal	9/11/39		28	134/84	9/25/39		27	134/86
		4/20/40		30	120/80	4/20/40		25	122/84
J. S. (M, 46) 131 lbs.	Acrocyanosis of feet					10/16/39	21	19	126/88
						10/18/39		20	132/84
						10/30/39	16*	12	124/86
						11/ 1/39	17*	14	118/84
						11/ 3/39	20*		112/84
						11/ 6/39	20*	19	124/84
						11/10/39	22*	20	126/90
						11/17/39	21*	20	122/88
						11/27/39	18*	17	120/84
						11/29/39	19*	17	112/86
		12/22/39		30	124/86	12/22/39	20*		122/86
		1/ 5/40		34	114/80	1/ 5/40	20*		114/82
						1/ 8/40	26*	22*	136/84
B. B. (F, 44) 114 lbs.	Scleroderma	1/13/40	26	30	152/92				
		1/22/40	22	31*	164/96				
		1/24/40	25		106/84	1/24/40	14		106/84
		2/ 5/40	18*		112/92	2/ 5/40	15		112/92
		2/ 9/40		22*	114/88	2/ 9/40	13		114/88
F. G. (M, 32) 170 lbs.	Raynaud's disease	3/ 4/40	23	30	138/80				
		3/ 8/40	26	31	146/80				
		3/25/40	22*	26	134/70				
		3/27/40	24*	32	136/84				
		3/29/40	22*		128/94	3/29/40		22	128/94
		4/18/40		29*	112/82	4/18/40		19	112/82
		4/22/40	23*	29*	132/82				
F. H. (M, 38) 215 lbs.	Scleroderma	3/20/40	30	26	132/96				
		6/ 3/40	30*	31	106/68				

* Denotes sympathectomized limb.

TABLE VII—*Continued*

SUBJECT (SEX, AGE, WEIGHT)	DIAGNOSIS	FOREARMS				CALVES			
		Date	Blood Flow, cc./100 cc./min.		Arterial Pressure	Date	Blood Flow, cc./100 cc./min.		Arterial Pressure
			Left	Right			Left	Right	
					mm. Hg				mm. Hg
C. M. (F, 29) 120 lbs.	Raynaud's disease	4/25/40	27	28	118/76				
		5/ 3/40	23*	36	130/82				
		5/15/40	27*	27*	116/76				
R. P. (F, 49) 130 lbs.	Raynaud's disease	7/15/39		28	136/96				
		7/27/39		24*	118/86				
B. B. (F, 33) 101½ lbs.	Hypertension					5/30/39		24	178/124
						6/ 9/39		17*	162/112
						6/12/39	14		156/110
						6/21/39		17*	158/118
						6/23/39	17*		152/116
E. E. (F, 38) 128½ lbs.	Hypertension					6/ 7/39		32	186/144
						6/26/39		31*	182/146
	After sympathectomy					7/ 5/39	19*		128/106
						7/ 7/39		20*	126/106
		7/ 8/39		38	126/108				
		9/27/39		40	118/102	9/27/39		21*	118/102
		10/ 2/39		42	122/98	10/ 2/39	25*		118/100
		4/ 8/40		41	116/100	4/ 8/40		31*	116/100
						4/10/40	21*		112/94
S. G. (M, 30) 139½ lbs.	Hypertension	12/ 6/39		48	202/158	12/ 6/39		39	202/158
						12/ 8/39	40		206/148
						12/13/39	38	40	194/148
		12/15/39		43	206/160	12/15/39		38	202/150
						12/29/39	42*	38	220/174
		1/ 3/40		39	234/172	1/ 3/40	35*		234/172
		1/10/40		44	218/166	1/10/40	41*		218/166
		1/31/40		47	218/176	1/31/40		37*	218/176
		2/ 7/40		37	214/176	2/ 7/40	36*		214/176
T. R. (F, 38) 115 lbs.	Hypertension	5/ 8/39		39	166/116	5/10/39		33	162/120
						5/17/39		24	164/116
						5/26/39		24*	200/146

TABLE VII—*Concluded*

SUBJECT (SEX, AGE, WEIGHT)	DIAGNOSIS	FOREARMS				CALVES			
		Date	Blood Flow, cc./100 cc./min.		Arterial Pressure	Date	Blood Flow, cc./100 cc./min.		Arterial Pressure
			Left	Right			Left	Right	
					mm. Hg				mm. Hg
T. R. (F, 38) 115 lbs.—*Continued*	Hypertension	5/29/39		35	198/146				
						6/ 1/39	25		212/146
						6/15/39	23*		166/124
		6/19/39		33	174/134	6/22/39		22*	176/134
		10/ 4/39		39	174/126	10/ 4/39		29*	174/126
						10/ 9/39	27*	24*	160/120
		6/12/40		32	164/116	6/12/40		26*	164/116
B. H. (F, 21) 123 lbs.	Hypertension	4/17/39	59		208/142				
		4/21/39	56		192/136				
H. F. (F, 36) 102 lbs.	Hypertension	3/17/39	47		228/150				
		9/20/39	27		256/182	9/20/39	29		256/182
		9/22/39	30		244/178	9/22/39	30		244/178
C. H. (M, 46) 144 lbs.	Hypertension					10/20/39		22	176/128
						10/23/39		23	174/136
						3/14/40		34	196/142
M. J. L. (F, 30) 177 lbs.	Hypertension	2/12/40		35	156/118	2/12/40		26	156/118
		2/14/40		36	148/114	2/14/40		26	148/114
		3/ 6/40		32	146/110	3/ 6/40		26	146/110
N. S. (F, 41) 148 lbs.	Hypertension	11/20/39		44	142/100	11/20/39		25	142/100
		11/22/39		36	134/102	11/22/39		23	134/102
	Nephrectomy	12/12/39		35	124/92	12/12/39		19	124/92
		6/17/40		36	126/96	6/17/40		26	126/96
M. W. (M, 26) 133½ lbs.	Unilateral chronic pyelonephritis	1/26/40		33	132/92	1/26/40		23	132/92
	After nephrectomy	1/29/40		34	130/88	1/29/40		24	130/88
		6/10/40		40	118/86	6/10/40		30	118/86
E. W. (F, 38) 141 lbs.	Hypertension	12/ 2/39		43	142/120	12/ 2/39		26	142/120
		5/25/40		34	144/116	5/25/40		30	144/116

subjects the maximum variations were 0 cc. to 11 cc./100 cc./min. (0 to 46 per cent).

Comparison of Blood Flow in Contralateral Limbs. The reactive-hyperemia blood flow was usually approximately the same in contralateral limbs but in certain individuals a considerable difference between the two sides was noted (Table VIII).

Simultaneous determinations of blood flow to the two forearms were made in four normal subjects and in four patients with peripheral vascular disease presumably not involving the muscle. In six of the eight subjects the difference between the two sides varied from 1 cc. to 4 cc./100 cc./min. (3.7 to 15.4 per cent). In the other two, differences of 5 cc. and 7 cc./100 cc./min. (13.5 and 30.4 per cent) were found.

Simultaneous reactive-hyperemia blood flows to the two normally innervated calves differed as follows: one normal subject, difference 2 cc./100 cc./min. (8 per cent); one patient with acrocyanosis of feet, difference 2 cc./100 cc./min. (9.5 per cent); one hypertensive patient, difference 2 cc./100 cc./min. (5.3 per cent).

The differences in reactive-hyperemia blood flow to contralateral limbs did not appear to be significantly affected by sympathectomy.

In the patient who manifested a difference of 7 cc./100 cc./min. (30.4 per cent) in the blood flow to the two normally innervated forearms, a difference of 6 cc./100 cc./min. (26.1 per cent) persisted after both forearms had been sympathectomized. In another patient there was a difference of 1 cc./100 cc./min. in reactive-hyperemia blood flow to the two forearms before sympathectomy and no difference afterward. In the patient with acrocyanosis of the feet, there was a difference of 2 cc./100 cc./min. in blood flow to the normally innervated calves, and a difference of 4 cc./100 cc./min. in the blood flow to the calves after lumbar sympathectomy. In the patient with hypertension who showed a difference of 2 cc./100 cc./min. in the reactive hyperemia blood flows to the calves before sympathectomy, there was a difference of 3 cc./100 cc./min. afterward.

No explanation was apparent for the occasional considerable difference in blood flow to contralateral limbs. Physical and X-ray examination of the forearms of the patient in whom there was, even after sympathectomy, a difference of 6 cc./100 cc./min. in blood flow to the two sides, revealed no detectable difference either in the vascular tree or in the proportions of muscle, bone and subcutaneous tissue in the two limbs.

Comparison of the Blood Flow to the Forearm and to the Calf in the

TABLE VIII

Reactive-Hyperemia Blood Flow Simultaneously Determined in Contralateral Limbs

SUBJECT	DIAGNOSIS	FOREARMS					CALVES				
		Blood Flow, cc./100 cc./min.		Arterial Pressure	Difference in Blood Flow on the Two Sides		Blood Flow, cc./100 cc./min.		Arterial Pressure	Difference in Blood Flow on the Two Sides	
		Left	Right		cc./100 cc./min.	Per cent	Left	Right		cc./100 cc./min.	Per cent
				mm. Hg					mm. Hg		
A. J.	Normal	26	28	126/78	2	7.7					
S. K.	Normal	31	33	140/88	2	6.4					
M. K.	Normal	30	27	138/84	3	11.1					
C. W.	Normal	37	42	120/78	5	13.5					
P. P.	Normal (torn right brachial plexus)	38	48*	112/78	10	26.4					
W. O.	Normal						25	27	134/86	2	8.0
B. B.	Scleroderma	26	30	152/92	4	15.3					
		22	31*	164/96	9	40.8					
F. G.	Raynaud's disease	23	30	138/80	7	30.4					
		26	31	146/80	5	19.2					
		22*	26	134/70	4	18.1					
		24*	32	136/80	8	33.3					
		23*	29*	132/82	6	26.0					
F. H.	Scleroderma	30	26	132/96	4	15.3					
		30*	28	106/68	2	6.7					
J. S.	Acrocyanosis of feet						21	19	126/88	2	10.5
							16*	12	124/86	4	33.3
							17*	14	118/84	3	21.4
							20*	19	124/84	1	5.3
							22*	20	126/90	2	10
							21*	20	122/88	1	5
							18*	17	120/84	1	5.9
							19*	17	112/86	2	11.7
							26*	22*	136/84	4	18.2
C. M.	Raynaud's disease	27	28	118/76	1	3.7					
		23*	36	130/82	13	56.6					
		27*	27*	116/76	0	0.0					
S. G.	Hypertension						38	40	198/148	2	5.3
							42*	38	220/174	4	10.5
T. R.	Hypertension						27*	24*	160/120	3	12.5

* Sympathectomized limb.

Same Subject. In thirty-seven of forty-one subjects the reactive-hyperemia blood flow to the forearm exceeded the blood flow to the calf by a substantial amount, which in the normal group varied from 6 to 16 cc./100 cc./min. In only one subject (normal) did the reactive-hyperemia blood flow to the calf exceed that to the forearm. In three subjects the blood flow to calf and forearm were approximately equal.

Average Values. Following the standard five-minute ischemia, the reactive-hyperemia blood flow to twenty-eight forearms of twenty subjects with normal arterial pressure and no detectible vascular disease of the muscle, varied from 24 to 42 cc./100 cc./min. and averaged 31 cc./100 cc./min. The blood flow to eighteen calves of a similar group of fourteen subjects varied from 14 to 38 cc./100 cc./min. and averaged 23 cc./100 cc./min.

There was no apparent explanation for this wide variation from subject to subject. The differences could not be related directly to sex or weight. Since most of the subjects were in the same age group, no analysis could be made of the possible influence of age. But even in subjects of the same age, sex, and weight, considerable differences in blood flow were found. These differences could not be explained by the shape or volume of the muscular segment, nor by the relative proportions of skin, subcutaneous tissue, muscle or bone, as determined by physical or X-ray examination. For example, two normal young men had right calves of comparable size (volumes of the segments in the plethysmographs, 1600 cc. and 1700 cc., respectively). Physical and X-ray examination of these two legs revealed no significant differences. The arterial pressure was 122/84 mm. Hg in both subjects. The reactive-hyperemia blood flow to the calf of one was 38 cc./100 cc./min., and of the other, 25 cc./100 cc./min., a difference of 52 per cent.

In a patient who had sustained a tear of the right brachial plexus, the resultant atrophy in the arm seemed to involve chiefly the muscles. The volume of a 6½ inch segment of the atrophic right forearm was 405 cc., whereas a similar segment of the normal forearm was 680 cc. (68 per cent larger). The reactive-hyperemia blood flow to the whole atrophic segment (194 cc./min.) was less than that to the contralateral normal segment (258 cc./min.). But when these values were

calculated for the volumes involved, the reactive-hyperemia blood flow to the atrophic segment (48 cc./100 cc./min.) exceeded by 10 cc./100 cc./min., or 26 per cent, the blood flow to the normal segment.

DISCUSSION

Extensive and rapid variations occur in the blood flow to the hands, feet and digits (11, 12, 13, 14). Such variations may be caused by changes in environmental temperature, by "vasomotor" stimuli, or by circulating humoral substances such as epinephrin. In addition, many unexplainable variations occur, which make the distal part of an extremity an undesirable location for measuring the "peripheral resistance" to blood flow.

In the resting forearm and calf, the blood flow is less variable than in the more distal parts (6, 14), and the threshold of reactivity to stimuli is higher. Nevertheless, even in the muscular segments considerable variations in blood flow may occur under the influence of vasoconstrictor and vasodilator stimuli (2). The present study indicates that most of these variations may be reduced or eliminated when the blood flow to the muscular segments is measured during the initial phase of reactive hyperemia.

The reactive-hyperemia blood flow is practically unaffected by heating the body and is very little affected by heating the segment enclosed within the plethysmograph. It is altered only slightly, if at all, by the milder vasoconstrictor stimuli which reduce markedly the blood flow to the hands, feet and digits, and which reduce considerably the blood flow to the resting forearm and calf. Severe and disagreeable vasoconstrictor stimuli may cause an appreciable reduction in the reactive-hyperemia blood flow, but strong vasodilator stimuli cause no increase in the flow except when there is a concomitant increase in arterial pressure. The level of the reactive-hyperemia blood flow is not increased following sympathectomy.

The reactive-hyperemia blood flow varies with the arterial pressure (5). Although it is appreciably influenced by certain other factors, the variations rarely exceed 30 per cent, and are usually not greater than 10 to 20 per cent. Such variations are small when compared with those which may be observed in the resting blood flow to the same parts.

The five-minute period of circulatory arrest, employed in these studies, may not produce a complete physiologic vasodilatation but the evidence indicates that such a state is closely approximated. Since the vasodilatation is relatively complete, is reproducible, and is relatively independent of vasomotor activity, the measurement of the reactive-hyperemia blood flow should furnish valuable information concerning the degree of organic constriction of the peripheral blood vessels.

SUMMARY

1. A relatively complete, and reproducible vasodilatation occurs in the muscular segment of a limb during the early phase of the reactive hyperemia which follows a five-minute period of circulatory arrest.

2. The blood flow measured during this vasodilatation—"reactive-hyperemia blood flow"—has the following characteristics:

(a) It is augmented with the first three to four successive determinations.

(b) It is relatively unaffected by full peripheral reflex vasodilatation.

(c) It is only slightly increased by local heat to 40°C.

(d) It is only slightly increased by prolonging the period of ischemia from 5 minutes to 10 or 15 minutes.

(e) It is not affected by mild vasoconstrictor stimuli, but may be altered by strong vasoconstrictor stimuli.

(f) It is not changed by vasodilator stimuli unless the stimulus causes an alteration in arterial pressure.

(g) Under basal conditions it is not increased following preganglionic sympathectomy.

(h) It is not affected by sleep, natural or induced.

(i) It varies directly with changes in arterial pressure (unless local vasoconstriction offsets the effect of the change in arterial pressure).

3. When measured under standard basal conditions, the reactive-hyperemia blood flow to 28 forearms of 20 subjects with normal arterial pressure varied from 24 cc. to 42 cc./100 cc./min. (average 31 cc./100 cc./min.); that to 18 calves of 14 subjects with normal arterial pressure, varied from 14 cc. to 38 cc./100 cc./min. (average 23 cc./100 cc./min.).

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BIBLIOGRAPHY

1. Lewis, T., and Grant, R., Observations upon reactive hyperemia in man. *Heart*, 1925, **12**, 73.
2. Wilkins, R. W., and Eichna, L. W., Blood flow to the forearm and calf. I. Vasomotor reactions: rôle of the sympathetic nervous system. *Bull. Johns Hopkins Hosp.*, 1941, **68**, 425.
3. Doupe, J., Newman, H. W., and Wilkins, R. W., The effect of peripheral vasomotor activity on systolic arterial pressure in the extremities of man. *Jour. Physiol.*, 1939, **95**, 244.
4. Hines, E. A., Jr., and Brown, G. E., A standard test for measuring the variability of blood pressure: its significance as an index of the prehypertensive state. *Ann. Int. Med.*, 1933, **7**, 209.
5. Wilkins, R. W., and Eichna, L. W., Blood flow to the forearm and calf. III. The effect of changes in arterial pressure on the blood flow to limbs under controlled vasodilatation in normal and hypertensive subjects. *Bull. Johns Hopkins Hosp.*, 1941, **68**, 477.
6. Abramson, D. I., and Ferris, E. B., Jr., Responses of blood vessels in the resting hand and forearm to various stimuli. *Amer. Heart Jour.*, 1940, **19**, 541.
7. Grant, R. T., and Pearson, R. S. B., The blood circulation in the human limb; observations on the differences between the proximal and distal parts and remarks on the regulation of body temperature. *Clin. Sci.*, 1938, **3**, 119.
8. Alam, M., and Smirk, F. H., Observations in man upon a blood pressure raising reflex arising from the voluntary muscle. *J. Physiol.*, 1937, **89**, 372.
9. Allen, E. V., and Adson, A. W., Comments on the surgical treatment of essential hypertension. *Proc. Staff Meet. Mayo Clin.*, 1937, **12**, 588.
10. Eichna, L. W., and Wilkins, R. W., Blood flow to the forearm and calf. IV. Thyroid activity: observations on the relation of blood flow to basal metabolic rate. *Bull. Johns Hopkins Hosp.*, 1941, **68**, 512.
11. Wilkins, R. W., Doupe, J., and Newman, H. W., The rate of blood flow in normal fingers. *Clin. Sci.*, 1938, **3**, 403.
12. Burton, A. C., The range and variability of the blood flow in the human fingers and the vasomotor regulation of body temperature. *Amer. Jour. Physiol.*, 1939, **127**, 437.
13. Kunkel, P., and Stead, E. A., Jr., Blood flow and vasomotor reactions in the foot in health, in arteriosclerosis, and in thromboangiitis obliterans. *J. Clin. Invest.*, 1938, **17**, 715.
14. Kunkel, P., Stead, E. A., Jr., and Weiss, S., Blood flow and vasomotor reactions in the hand, forearm, foot and calf in response to physical and chemical stimuli. *J. Clin. Invest.*, 1939, **18**, 225.

BLOOD FLOW TO THE FOREARM AND CALF

III. The Effect of Changes in Arterial Pressure on the Blood Flow to Limbs under Controlled Vasodilatation in Normal and Hypertensive Subjects[1, 2]

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In essential hypertension the cardiac output, or total blood flow to the body, has not been found to be increased (1, 2). If the total blood flow is not increased, the total peripheral resistance to blood flow must be greater than normal, otherwise the increase in arterial pressure could not be maintained. A number of investigators (3, 4, 5) have measured the blood flow to the limbs of normal and hypertensive subjects in an attempt to determine whether in hypertension the peripheral resistance is abnormal in these parts. They were unable to demonstrate that the blood flow to the limbs, even during strong vasodilatation, was significantly greater in the hypertensive than in the normal subjects. They therefore concluded that in hypertension there is an increased resistance to blood flow in the limbs, and that this resistance cannot be reduced to the normal level even by the use of methods which induce strong physiologic vasodilatation.

These conclusions are based upon the assumption that when the peripheral resistance remains unchanged, an elevation in arterial pressure will be accompanied by a significant increase in blood flow to the limbs. The experimental evidence supporting this assumption is incomplete. For example, it has not been shown that a correlation exists between arterial pressure and blood flow to the normal human limb during controlled vasodilatation. Until it has been demonstrated

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[2] Reported in a paper read at the annual meeting of The American Society for Clinical Investigation, May 6, 1940 (Jour. Clin. Investigation, 19, 770, 1940).

that in normal subjects an increase in arterial pressure causes the blood flow to rise to a level definitely above the normal, it does not seem justifiable to conclude that in hypertensive patients an apparently normal blood flow signifies an abnormal peripheral resistance.

In testing the validity of the aforementioned assumption, it is essential to control the state of vasodilatation in the parts in which the measurements of blood flow are to be made. After hypertension has become established, the circulation to all parts of the body is still subject, as before, to the metabolic and homeostatic needs of the body as a whole, and of the parts themselves. These needs may cause great variations in local blood flow (i.e., in local resistance) in any part selected for study. Previous studies (6, 7) have shown that a relatively complete and reproducible vasodilatation occurs in the muscular segments of the forearm and calf following a five minute period of circulatory arrest. This method of producing vasodilatation was employed in the present study.

This study was undertaken to answer the following questions concerning the relationship between arterial pressure and the blood flow to the forearm and calf *under controlled conditions of vasodilatation:* (a) Is the plethysmographic method capable of detecting changes in blood flow when the arterial pressure is raised or lowered? (b) In a given subject, is there a direct relationship between arterial pressure and blood flow? (c) If such a relationship exists, does it hold for both normal and hypertensive subjects? (d) Is there a difference between the blood flow in hypertensive patients, and the blood flow in normal persons whose arterial pressure has been raised to hypertensive levels? (e) Is there a difference between the blood flow in normal persons, and the blood flow in hypertensive patients whose arterial pressure has been lowered to normal levels? (f) Is the blood flow under basal conditions in a group of hypertensive subjects greater than in a group of normal subjects? The experiments which are about to be described afford affirmative answers to the first three of these questions. But the last three questions, which bear upon the problem of the peripheral resistance in hypertension, can be answered only with reservations.

METHODS

The blood flow to the forearm and calf was measured plethysmographically during the first 5 to 15 seconds of reactive hyperemia following the release of the

circulation after a 5 minute period of arterial occlusion (7). The subjects had been previously warmed to induce reflex vasodilatation (6). The water in the plethysmograph was kept at 32°C. During each determination of blood flow, the arterial pressure was measured in a free extremity by the auscultatory method, using a wide cuff and a mercury manometer.

After the control level of reactive-hyperemia blood flow was established, measurements were made during and after procedures designed temporarily to raise or lower the arterial pressure. The pressor procedures included the immersion of a hand or foot in iced water (8), the solving of an arithmetical problem, the exercise of an ischemic arm (9), and the administration of paredrinol sulfate[3] (25 to 35 mgm., intramuscularly). The depressor procedures included the administration of narcotic doses of sodium amytal (0.2 gram by mouth every hour for 3 doses), and the sudden release of blood pressure cuffs which had been occluding the circulation through both thighs for 5 to 10 minutes.

In many patients, studies of the blood flow were made on subsequent days when, in the natural course of the disease or as a result of therapy, changes in arterial pressure had occurred.

Most of the subjects in both the normal and hypertensive groups (Tables I and II) were relatively young adults. Young patients were preferred because it was believed that the results would be less likely to be modified by the vascular changes which are associated with advancing age.

The criteria which determined the selection of the hypertensive patients were: (a) persistent and usually severe hypertension, (b) absence of a history of antecedent bilateral renal disease. All of these patients when they first came under observation were believed to have "essential hypertension". Whether they were still to be considered as cases of essential hypertension, after the studies had been completed, depends upon one's definition of this disease. For example, the discovery of unilateral renal disease in three of the patients (M. W., E. W., and N. S.) (Table I) places them in a category rather different from that of the usual case of essential hypertension. In two other patients (H. F. and B. H.) there was a considerable reduction in renal function as measured by the urea clearance test. In one of these cases (H. F.)[4] it is known that there was no albuminuria and no detectable reduction in renal function at an earlier stage of the disease. In the other case (B. H.) the antecedent history was obscure; clinical diagnosis was "malignant hypertension". No specific details of the other cases will be given, with the exception of the data presented in Table I, from which it may be gathered

[3] Kindly supplied by the Smith, Kline and French Laboratories.

[4] This case has been reported in greater detail elsewhere (Bordley, J., III, and Eichna, L. W.: A Photographic Study of the Evolution of the Retinal Lesions in Cases of Arterial Hypertension. *Trans. Assoc. American Physicians*, **55**, 270, 1940). For comparison with the earlier report it should be stated that the first measurements of blood flow in this case (Table I) were made in March, 1939, the second measurements (Table IV) in September, 1939.

TABLE I

Patients with Hypertension

SUBJECT (SEX, AGE) WEIGHT	ARTERIAL PRESSURE (MM. Hg)		EYE GROUND CHANGES	URINALYSIS	N.P.N.	P.S.P. 2 HR. EX.	UREA CLEAR., % NORM	URINE CONC., MAX. SP. GR.	ELECTROCARDIOGRAM	TELEOROENTGENOGRAM, CARDIAC OUTLINE	VITAL CAPACITY, % NORM.	VENOUS PRESSURE (MM. SALINE)	REACTIVE HYPEREMIA, BLOOD FLOW, CC./100 CC./ MIN.	
	Lowest	Highest											Fore-arm	Calf
					mg. %	%								
B. B. (F, 33) 101 lbs.	164/102	220/135	Minimal sclerosis of arteries	Albumin 0; 1 hyalin cast	28	70	102	1.022	Normal record	M.R. 3.2; M.L. 6.7; A. 4; T. 24			37	20
M. C. (F, 52) 132 lbs.	148/94	164/106	Moderate sclerosis of arteries	Albumin trace; occ. gran. cast	31	80	52	1.023	Levogram, low R V	M.R. 4; M.L. 10; A. 5.5; T. 26.5	88	80	34	21
E. E. (F, 38) 129 lbs.	184/124	238/158	Blurred discs, exudates, narrow irregular arteries	Albumin trace; occ. R.B.C.	38	81	95	1.022	Low T I and T II	M.R. 5.0; M.L. 9.0; A. 7.5; T. 27.6	89	110	46	31
H. F. (F, 36) 102 lbs.	220/144	262/170	Papilledema, exudates, hemorrhages, marked sclerosis	Albumin trace	32	68	45	1.022	T I inverted	M.R. 5.0; M.L. 9.7; A. 5.5; T. 26.1	89	67	47	31
S. G. (M, 30) 140 lbs.	192/130	236/170	Papilledema, exudates, hemorrhages, marked sclerosis	Albumin 1+; occ. R.B.C. casts	38	54	75	1.022	Low T I	M.R. 3.8; M.L. 8.0; A. 5.8; T. 29.4	114	77	44	40
B. H. (F, 21) 123 lbs.	190/120	245/170	Papilledema, exudates, hemorrhages	Albumin 3+; occ. R.B.C. casts	44	49	31	1.016	Dextrogram; biphasic T V	M.R. 3.0; M.L. 8.5; A. 5; T. 27.5	106	84	57	39
C. H. (M, 46) 144 lbs.	160/100	198/124	Narrow opaque arteries	Albumin 1+	33	40	76		Levogram; low T I and T II; biphasic T V	M.R. 3.9; M.L. 9.4; A. 5.7; T. 27.5		40	49	34
M. L. (M, 37) 172 lbs.	184/100	234/140	Blurred discs, narrowed arteries	Normal urine	36	57	112	1.026	Levogram; low R V; P-R interval 0.21	M.R. 4.2; M.L. 12.2; A. 5.4; T. 33.2	76	120	32	22

M. N. (F, 39) 133 lbs.	170/110	278/158	Arteries narrowed and tortuous	Albumin 1+	36	67	93	1.030	Normal	M.R. 4.0; M.L. 8.9; A. 5; T 25.5			37	25
T. R. (F, 38) 115 lbs.	154/106	200/128	Narrowed, somewhat irregular arteries	Albumin 0; rare cast and R.B.C.	39	85	60	1.023	Low R V	M.R. 3.7; M.L. 6.6; A. 4.4; T. 25.6	118	100	40	30
E. W. (F, 50) 101 lbs.	176/120	214/166	Minimal sclerosis of arteries	Normal urine		85			T II biphasic; T III sharply inverted	"Heart within normal limits"			32	23
M. L. (F, 30) 177 lbs.	138/94	176/114	Arteries narrow with increased light streak	Normal urine	26	64	128	1.028	Low T V, levogram	M.R. 3.2; M.L. 10; A. 4.8; T. 30		95	35	26
N. S. (F, 41) 148 lbs.	150/96	180/105	Normal fundi	Albumin 1+; rare R.B.C. and cast	32	50	69	1.020	Low T I and T II	M.R. 4.3; M.L. 9.2; A. 5.2; T. 28.5	60	135	44	25
M. W. (M, 26) 134 lbs.	196/130	212/150	Blurred disc margin, exudates, arteriosclerosis	Albumin 1+; occ. R.B.C. and cast	29	67	92	1.028	Low T I and T II	M.R. 4.8; M.L. 7.2; A. 5.9; T. 29.5		100	44	34
E. W. (F, 38) 101 lbs.	154/96	256/160	Minimal narrowing of arteries	Normal urine	32	54			Levogram	M.R. 3.6; M.L. 8.7; A. 5.3; T. 24.3			40	33
S. K. (F, 44) 165 lbs.	200/108	222/136	Narrowed arteries, exudates	Albumin 0; rare R.B.C. and cast	28	56			Levogram; inverted T I, T II, T V	M.R. 6.3; M.L. 9.9; A. 5.5; T. 29		75	35	24

that the findings in some instances were those usually encountered in cases with a relatively benign type of hypertension, while in others the findings were those usually associated with a more severe (malignant) type of hypertension.

In all patients with sympathectomized limbs, preganglionic sympathectomy had been performed. The criteria for the completeness of the sympathectomy were

TABLE II

Normal Subjects and Patients with Normal Arterial Pressure

SUBJECT (SEX, AGE, WEIGHT)	DIAGNOSIS	ARTERIAL PRESSURE (MM. Hg)		REACTIVE HYPEREMIA, BLOOD FLOW, CC./100 CC./MIN.	
		Lowest	Highest	Forearm	Calf
R. N. (M, 26) 180 lbs.	Normal	118/74	126/84	30	
W. O. (M, 26) 178 lbs.	Normal	118/74	146/96	30	25
J. H. (M, 28) 185 lbs.	Normal	114/74	126/88	37	24
M. P. (M, 24) 156 lbs.	Normal	118/76	130/86	34	38
P. P. (M, 35)	Normal	110/74	112/78	38	
M. K. (M, 29) 122 lbs.	Normal	138/84	138/84	30	
S. K. (M, 39) 130 lbs.	Normal	134/80	144/96	32	22
P. F. (M, 28) 162 lbs.	Normal	114/74	124/76		30
R. H. (F, 29)*	Ingestion $HgCl_2$	116/76	122/80	29	14
W. J. (M, 36)* 235 lbs.	Lobar pneumonia	126/78	144/96	30	26
S. W. (F, 21)* 118 lbs.	Gonorrheal arthritis	102/64	110/78	30	20
A. J. (M, 21)* 160 lbs.	Lobar pneumonia	120/74	130/90	27	
C. W. (M, 34)* 145 lbs.	Lobar pneumonia	114/68	124/74	42	
T. J. (M, 29) 168 lbs.	Thromboangeitis obliterans of feet only	118/76	124/90	32	15
J. S. (M, 46) 131 lbs.	Acrocyanosis of feet	110/70	136/92	34	21
B. C. (F, 28)* 131 lbs.	Hypochromic microcytic anemia	100/60	108/80	36	24
B. B. (F, 44) 114 lbs.	Scleroderma hands, forearms	104/78	114/92	26	15
F. H. (M, 38) 215 lbs.	Scleroderma hands	106/66	138/96	30	
R. P. (F, 49) 130 lbs.	Raynaud's hands, feet	118/84	140/104	24	
F. G. (M, 32) 170 lbs.	Raynaud's hands, feet	108/70	148/102	29	22
C. M. (F, 29) 120 lbs.	Raynaud's hands, feet	102/76	132/88	28	
R. B. (F, 18)* 112 lbs.	Tbc. pleurisy, effusion	138/88	146/98		25

* Patient convalescing when studied.

those used in a previous study (6). There was no evidence of vascular disease in the parts where the measurements were made. In this group there were patients with normal arterial pressure and patients with hypertension. The results obtained in this group of patients formed a background for the studies on subjects with normally innervated extremities in which the activity of the sympathetic nervous system had to be taken into account.

Definitions. As used in this paper the expression "basal arterial pressure" refers to the arterial pressure measured under basal conditions without reference to any particular experiment. The "mean arterial pressure" was obtained by taking one-half the sum of the systolic and diastolic pressures. This arithmetical mean was used for the sake of convenience; it is realized that it does not accurately represent the physiological mean. The expressions "reactive-hyperemia blood flow" and "resting blood flow" have been explained in a previous paper (7).

RESULTS

Alterations in Blood Flow During Induced Changes In Arterial Pressure

(a) *Subjects with Sympathectomized Limbs.* When the procedures designed to change the arterial pressure failed significantly to do so, the reactive-hyperemia blood flow to the forearm or calf showed no significant change. However, when the arterial pressure was raised, the blood flow increased; and when the arterial pressure was lowered, the blood flow decreased (Tables III and IV). Figure 1 shows the results obtained in the sympathectomized forearm of a subject with normal arterial pressure. In this case, a linear relationship between arterial pressure and blood flow was found (Fig. 2).

Similar alterations in the reactive-hyperemia blood flow, during changes in arterial pressure, were found in hypertensive subjects (Table IV). Figure 3 shows the results obtained in a patient with essential hypertension who was subjected to splanchnic and lumbar sympathectomy. The correlation between arterial pressure and the blood flow to the sympathectomized right calf is shown in Figure 4. The second-stage (left) sympathectomy was followed by a marked fall in the basal arterial pressure and a corresponding decrease in the reactive-hyperemia blood flow to the right calf. At this time pressor stimuli still produced temporary increases in the blood flow which showed a direct, linear correlation with the arterial pressure (Fig. 4).

(b) *Subjects with Normally-Innervated Limbs.* In the normally innervated limbs of most subjects (the exceptions will be mentioned later), alterations in the reactive-hyperemia blood flow corresponded with changes in arterial pressure, even during strong sensory pressor stimuli (Tables III and IV). Figure 5 shows the results obtained in a normal subject. It is interesting that the direct relationship between arterial pressure and reactive-hyperemia blood flow (Fig. 6) was found to hold also during the rise of arterial pressure induced by the adminis-

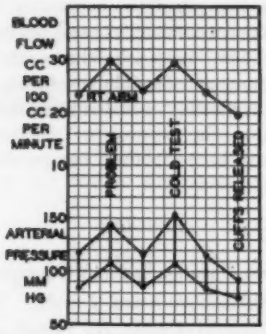

FIG. 1. Chart of arterial pressure and of reactive-hyperemia blood flow to the forearm obtained in an experiment on a patient (R. P.) who had had a bilateral cervical, preganglionic sympathectomy for Raynaud's disease of the hands. Rises of arterial pressure induced by mental arithmetical problem, and by immersion of a hand in iced water; a fall of arterial pressure induced by sudden release of blood pressure cuffs on both thighs where they had been occluding the circulation for 6 minutes.

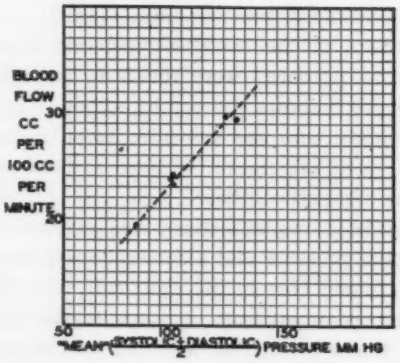

FIG. 2. Graph obtained by plotting each reactive-hyperemia blood flow against the "mean" arterial pressure at the time of the flow. Data from experiment shown in Fig. 1.

tration of paredrinol, a drug which some workers believe produces a type of hypertension similar to essential hypertension (10).

The same correlation between reactive-hyperemia blood flow and

arterial pressure was found in the normally innervated limbs of some hypertensive patients (Table IV). Figure 7 illustrates the results obtained in a patient in whom the removal of a pyelonephritic left kidney was followed by a marked fall in the basal arterial pressure, and a corresponding decrease in reactive-hyperemia blood flow. In both the forearm and the calf, regardless of the level of the basal arterial pressure, pressor stimuli induced changes in blood flow which showed a linear correlation with the simultaneously determined arterial pressure (Fig. 8). In this case a direct, though not an exactly linear, relationship held when a rise in pressure was induced post-operatively by paredrinol.

Effect of Prolonged Changes in Arterial Pressure. In four hypertensive patients the basal arterial pressure was materially reduced for at least several months following therapeutic operative procedures (nephrectomy or splanchnic and lumbar sympathectomy). These reductions of arterial pressure were immediately accompanied by corresponding decreases in the reactive-hyperemia blood flow to the forearm and calf (Table V). The results obtained in two such patients have been mentioned above, and have been shown in Figures 3, 4, 7 and 8. In five hypertensive patients similar operative procedures failed to lower the basal arterial pressure, and the reactive-hyperemia blood flow to the forearm and calf remained unchanged.

Changes in arterial pressure occurring in the course of other diseases were also accompanied by corresponding changes in the reactive-hyperemia blood flow. Other investigators have reported changes in blood flow in the course of acute glomerulo-nephritis (11, 12). Since their studies of blood flow were made in skin areas which are considerably affected by alterations in body temperature, it was of interest to determine whether similar changes in blood flow could be detected in the muscular segments of the limbs. In the one case of acute glomerulo-nephritis which was completely studied, a direct correlation between the arterial pressure and the reactive-hyperemia blood flow was observed (Table V).

In patients with Addison's disease, treatment with desoxycorticosterone brought about a rise in basal arterial pressure and a corresponding increase in the reactive-hyperemia blood flow (Table V). In one patient, hypertension followed the implantation of pellets of

TABLE III

Alteration of Reactive-Hyperemia Blood Flow with Arterial Pressure Change in Subjects with Normal Arterial Pressure

SUBJECT (SEX, AGE)	DIAGNOSIS	RESTING STATE			COLD TEST			MENTAL PROBLEM			PAREDRINOL SULFATE		
		Blood Flow, cc./100 cc./min.		Arterial Pressure	Change in Blood Flow, cc./100 cc./min. and %		Rise in Arterial Pressure, mm. Hg and %	Change in Blood Flow, cc./100 cc./min. and %		Rise in Arterial Pressure, mm. Hg and %	Change in Blood Flow, cc./100 cc./min. and %		Rise in Arterial Pressure, mm. Hg and %
		Arm	Calf		Arm	Calf		Arm	Calf		Arm	Calf	
				mm. Hg									
R. H. (F, 29)	Normal	29	14	116/76	5 17.2%	6 42.7%	30/38 35.4%	7 24.1%	5 35.7%	20/22 21.9%	9 31.0%	8 57.0%	72/26 51.0%
R. N. (M, 26)	Normal	31		124/74	7 22.6%		34/32 28.3%						
W. O. (M, 26)	Normal	28		134/84	−3 −10.7%		10/18 12.8%						
		30	25	120/82	4 13.3%	6 23.9%	24/26 24.8%						
M. P. (M, 24)	Normal		37	118/80		7 18.9%	20/20 20.2%						
		33	38	122/84				5 15.1%	4 10.5%	10/14 11.7%			
S. W. (F, 21)	Normal	30	20	102/68	9 30.0%	2 10.0%	52/56 63.5%	0 0.0%	0 0.0%	12/4 9.4%	5 16.6%	8 40.0%	58/26 49.5%
T. J. (M, 29)	Normal	32		124/90	5 15.6%		30/18 22.4%						
J. S. (M, 46)	Normal	32		128/92	2 6.3%		6/4 4.6%						

J. S. (M, 46)	Normal	32		128/92	2 6.3%		6/4 4.6%						
		30		124/88	0 0.0%		24/22 21.7%	6 20.0%		14/10 11.3%			
		34		114/80	3 8.8%		24/26 25.8%	6 17.6%		28/24 26.8%			
R. B. (F, 18)	Normal		25	142/90		4 16.0%	20/22 18.1%		3 12.0%	14/0 6.0%			
W. J. (M, 36)	Normal	30	27	128/82							2 6.6%	2 7.4%	24/8 15.2%
Average.....	Normal	31	25	123/81	4.7 15.4%	5 22.3%	26/28 25.2%	4.5 14.5%	3 14.6%	15/11 14.5%	5 18.1%	6 34.8%	51/20 38.6%
F. G. (M, 32)	Raynaud's disease	23 L		138/80	6 26.0%		26/28 24.8%						
		30 R		138/80	9 30.0%		26/28 24.8%						
		24*L		136/84	2* 8.4%		2/6 3.6%	3* 12.5%		10/4 6.4%	4* 16.6%		32/12 20.0%
		32 R		136/84	3 9.4%		2/6 3.6%	8 25.0%		10/4 6.4%	11 34.4%		32/12 20.0%
		22*L	22	128/94							7* 31.8%	9 41.0%	28/10 17.1%
		29*R	19	112/82	8* 27.6%	4 21.0%	16/14 15.5%				2* 6.9%	5 26.3%	32/12 22.6%
		23*L		132/82	2* 8.7%		4/12 7.5%						
		29*R		132/82	3* 10.3%		4/12 7.5%						

* Sympathectomized limb.

L = left limb; R = right limb, when both were studied; all not marked, right.

— denotes a decrease; all other changes were increases.

TABLE III—*Continued*

SUBJECT (SEX, AGE)	DIAGNOSIS	RESTING STATE			COLD TEST			MENTAL PROBLEM			PAREDRINOL SULFATE		
		Blood Flow, cc./100 cc./min.		Arterial Pressure	Change in Blood Flow, cc./100 cc./min. and %		Rise in Arterial Pressure, mm. Hg and %	Change in Blood Flow, cc./100 cc./min. and %		Rise in Arterial Pressure, mm. Hg and %	Change in Blood Flow, cc./100 cc./min. and %		Rise in Arterial Pressure, mm. Hg and %
		Arm	Calf		Arm	Calf		Arm	Calf		Arm	Calf	
				mm. *Hg*									
R. P. (F, 49)	Raynaud's disease	28		136/96	8		24/24	4		18/12			
					28.5%		20.7%	14.3%		12.9%			
		24*		116/86	5*		38/22	6*		28/22			
					20.8%		29.7%	25.0%		24.8%			
T. J. (M, 29)	Buerger's disease (feet)		16*	124/90		6*	30/18						
						37.5%	22.4%						
J. S. (M, 46)	Acrocyanosis (feet)		17*L	118/84		4*	14/22						
						23.5%	17.8%						
			14 R	118/84		2	14/22						
						14.3%	17.8%						
			20*L	112/84		2*	2/2						
						10.0%	2.0%						
			18*L	120/84		5*	24/22					6*	28/12
						27.8%	22.6%					33.3%	19.6%
			17 R	120/84		5	24/22					5	28/12
						29.4%	22.6%					29.4%	19.6%
			19*L	112/86		4*	18/16						
						21.0%	17.2%						
			17 R	112/86		4	18/16						
						23.5%	17.2%						

			20*L	122/86		4*	26/24		6*	16/12			
						20.0%	24.0%		30.0%	13.5%			
			20*L	114/82		8*	24/24		8*	28/22			
						40.0%	24.5%		40.0%	25.6%			
			26*L	136/84					6*	12/20			
									23.0%	14.6%			
Average.....	Vascular disease (but not in part)	30	18	130/88	7	4	19/20	6		18/12	11	6	30/12
					22.9%	22.0%	17.4%	19.7%		12.9%	34.4%	32.3%	18.9%
	Limbs sympathectomized	25*	18*	121/86	4.3*	5.3*	24/18	5*	7*	24/20	4.3*	6*	30/12
					14.1%	30.6%	20.4%	18.8%	31.0%	21.3%	18.4%	33.3%	20.2%
B. C. (F, 28)	Hypochromic anemia (Hgb. 43%)	35	18	104/64	22	12	34/42				13	14	54/36
					63.0%	66.6%	45.2%				37.2%	77.8%	53.6%
	Same (Hgb. 53%)	33	18	106/80	11	7	46/44				10	10	32/14
					33.3%	38.9%	48.4%				30.3%	55.6%	24.8%
	Same (Hgb. 77%)	37	24	104/76	13	10	38/40				9	13	54/28
					35.2%	41.6%	43.3%				24.3%	54.3%	45.5%
F. W. (F, 42)	Pernicious anemia (Hgb. 63%)	33	22	112/78	11	6	26/20	3	2	12/6			
					33.3%	27.2%	24.2%	9.1%	9.1%	9.5%			
	Same (Hgb. 99%)	38	32	130/96	2	2	14/16						
					5.3%	6.3%	13.3%						
Average.....	Anemia	34	20	108/75	14	8	33/31	3	2	12/6	11	12	43/25
					40.7%	36.6%	35.5%	9.1%	9.1%	9.5%	33.7%	66.7%	39.2%
I, H. (F, 54)	Addison's disease	29	19	112/84	7	5	26/20						
					24.1%	26.3%	23.5%						

TABLE III—*Concluded*

SUBJECT (SEX, AGE)	DIAGNOSIS	RESTING STATE			COLD TEST			MENTAL PROBLEM			PAREDRINOL SULFATE		
		Blood Flow, cc./100 cc./min.		Arterial Pressure	Change in Blood Flow, cc./100 cc./min. and %		Rise in Arterial Pressure, mm. Hg and %	Change in Blood Flow, cc./100 cc./min. and %		Rise in Arterial Pressure, mm. Hg and %	Change in Blood Flow, cc./100 cc./min. and %		Rise in Arterial Pressure, mm. Hg and %
		Arm	Calf		Arm	Calf		Arm	Calf		Arm	Calf	
				mm. Hg									
E. L. (F, 51)	Addison's disease	26	14	112/78	3	3	26/34						
					11.5%	21.4%	31.6%						
		30	19	120/82	3	6	38/32						
					10.0%	31.6%	36.6%						
Average.....	Addison's disease	28	18	114/82	5	5	29/26						
					17.4%	26.4%	28.8%						
C. S. (M, 45)	Hyperthyroidism (B.M.R. +31%)	38	26	118/60	13	16	42/25	7	3	14/4			
					34.2%	61.5%	38.2%	18.4%	11.5%	10.1%			
	Same (B.M.R. +3%) (after thyroidectomy)	38	22	122/70	9	7	36/32	5	4	6/6			
					23.6%	31.8%	35.4%	13.1%	18.2%	6.3%			
	Same (B.M.R. −24%)	28	17	118/86	4	4	10/4	1	2	4/2			
					14.3%	23.5%	6.9%	3.6%	11.8%	2.9%			
E. E. (F, 38)	Sympathectomy for hypertension with relief	38		126/108	1		20/20	1		8/2			
					2.6%		17.1%	2.6%		4.3%			
		41	31*R	116/100	7	3*	18/12	3	2*	10/0	12	4*	24/8
					17.0%	9.7%	13.9%	7.3%	6.5%	4.6%	29.3%	12.9%	14.8%
		42 L	21*L	112/94	0	4*	10/12				23	11*	58/34
					0.0%	19.0%	10.7%				74.2%	52.5%	44.6%
			19*L	126/106		4*	14/12		−1*	0/−4			
						21.0%	11.2%		−5.3%	−1.7%			
			20*R	126/106		6*	26/20						
						30.0%	19.8%						

			20 K	120/100		30.0%	19.8%							

M. W. (M, 26)	Nephrectomy for hypertension with relief	33	23	132/92	8	11	32/36	4	2	8/6				
					24.2%	47.9%	30.4%	12.1%	8.7%	6.3%				
		34	24	130/88							20	21	78/26	
											58.9%	87.5%	47.6%	
		40	30	118/86	6	5	16/18	1	−1	6/−4	17	17	64/30	
					15.0%	16.7%	16.7%	2.5%	−3.3%	1.0%	42.5%	56.7%	46.0%	
N. S. (F, 41)	Nephrectomy for hypertension with relief	35	19	124/92	12	7	32/26	2	4	14/10				
					34.3%	36.8%	26.8%	5.7%	21.0%	11.1%				
		36	26	126/96	8	6	36/28	4	2	14/2				
					22.2%	23.0%	28.8%	11.1%	7.7%	7.2%				
Average.....	Postoperative relief of hypertension	37	25	123/95	7	7	25/25	2	2	10/3	18	19	56/25	
					18.1%	31.1%	21.7%	6.9%	8.5%	5.7%	51.2%	72.1%	38.2%	
			23*	120/102		4*	17/14		0.5*	5/−2		8*	41/21	
						19.9%	13.9%		0.6%	1.4%		32.7%	29.7%	
W. N. (M, 14)	Glomerulonephritis, convalescent	51	31	116/78	−6	−2	0/−2	−2	−1	4/2				
					−11.7%	−6.5%	−1.0%	−3.9%	−3.2%	2.1%				
		39	28	118/76							5	7	38/24	
											12.8%	25.0%	32.0%	
		43	36	114/76							25	20	58/38	
											58.2%	55.5%	50.5%	
			33	116/74								13	38/20	
												39.4%	30.6%	

TABLE IV

Alteration of Reactive-Hyperemia Blood Flow with Arterial Pressure Change in Patients with Hypertension

SUBJECT (SEX, AGE)	DIAGNOSIS	RESTING STATE			COLD TEST			MENTAL PROBLEM		
		Blood Flow, cc./100 cc./min.		Arterial Pressure, mm. Hg	Change in Blood Flow, cc./100 cc./min. and %		Rise in Arterial Pressure, mm. Hg and %	Change in Blood Flow, cc./100 cc./min. and %		Rise in Arterial Pressure, mm. Hg and %
		Arm	Calf		Arm	Calf		Arm	Calf	
B. B. (F, 33)	Hypertension	39		190/132	8		36/20	1		6/−6
					20.5%		17.4%	2.6%		0.0%
			24 R	178/124		−5	58/34		1	22/8
						−20.8%	30.4%		4.2%	9.9%
			14 L	156/110		0	46/32		0	16/8
						0.0%	29.3%		0.0%	10.5%
			17*R	158/118		2*	16/20		−2*	0/6
						11.8%	13.0%		−11.8%	2.2%
			17*L	152/116		4*	32/16		1*	8/8
						23.5%	17.9%		5.9%	6.0%
M. C. (F, 52)	Hypertension	34	18*L	146/106	16	6*	50/28	2	3*	20/12
					47.0%	33.3%	31.0%	5.8%	16.6%	8.7%
			22*L	146/104		4*	32/18			
						18.2%	20.0%			
E. E. (F, 38)	Hypertension	49		174/146	11		52/18	3		14/4
					22.5%		21.9%	6.1%		5.6%
			32 R	186/144		2	48/26		−1	12/10
						6.3%	23.1%		−3.1%	6.9%
			31*R	182/146		7*	40/14		1*	8/2
						22.6%	16.5%		3.2%	3.0%
			27 L	170/128		1	0/18		−2	−2/6
						3.7%	6.0%		−7.4%	2.7%

B. H. (F, 21)	Hypertension	59 L		208/142	13 22.0%		32/32 18.3%			
			39 L	204/146		4 10.3%	16/26 12.0%			
S. G. (M, 30)	Hypertension		40 R	198/148		2 5.0%	78/58 39.3%			
			38 L	198/148		8 21.0%	78/58 39.3%			
		48	39 R	202/158	−17 −35.2%	−10 −25.6%	78/54 36.7%			
		43	38 R	206/160	5 11.6%	−3 −7.9%	42/42 22.9%	2 4.7%	0 0.0%	−2/−2 −1.1%
		39	35*L	234/172	1 2.6%	9* 25.7%	46/44 22.2%			
		44	41*L	218/166	0 0.0%	9* 21.9%	58/46 27.0%			
			42*L	220/174		10* 23.8%	52/34 21.8%			
			38 R	220/174		−5 −13.2%	52/34 21.8%			
		47	37*R	218/176	−3 −6.4%	−1* −2.7%	8/12 5.1%			
T. R. (F, 38)	Hypertension		33 R	162/120		−4 −12.1	92/66 56.0%			
			24 R	164/116		0 0.0%	94/70 58.5%		5 20.8%	8/2 3.6%

* Sympathectomized limb.
L = left limb; R = right limb, when both were studied. All not marked, right.
− denotes a decrease; all other changes were increases.

TABLE IV—*Continued*

SUBJECT (SEX, AGE)	DIAGNOSIS	RESTING STATE			COLD TEST			MENTAL PROBLEM		
		Blood Flow, cc./100 cc./min.		Arterial Pressure, mm. Hg	Change in Blood Flow, cc./100 cc./min. and %		Rise in Arterial Pressure, mm. Hg and %	Change in Blood Flow, cc./100 cc./min. and %		Rise in Arterial Pressure, mm. Hg and %
		Arm	Calf		Arm	Calf		Arm	Calf	
T. R. (F, 38) (*cont.*)	Hypertension		24*R	200/146		6*	42/22			
						25.0%	18.5%			
			25 L	212/146		−4	64/34		−3	−28/−12
						−16.0%	27.4%		−12.0%	−11.2%
		35		198/146	1		48/28	−5		−8/−10
					2.9%		22.1%	−14.3%		−5.2%
		39	29*R	174/126	−13	7*	32/32			
					−33.4%	24.1%	21.3%			
		32	26*R	164/116	−4	10*	56/46			
					−12.5%	38.4%	36.4%			
			23*L	166/124		9*	54/32		0*	4/10
						39.1%	29.6%		0.0%	4.8%
			22*R	176/134		10*	38/54		−2*	−24/−8
						45.5%	29.7%		−9.1%	−10.3%
			27*L	160/120		11*	52/42			
						40.8%	33.6%			
			24*R	160/120		12*	52/42			
						50.0%	33.6%			
		33		174/134				−4		0/2
								−12.1%		0.7%
C. H. (M, 46)	Hypertension	50	34	196/142	0	3	22/22	−5	−2	0/10
					0.0%	8.8%	13.0%	−10.0%	−5.9%	3.0%

M. L. (M, 37)	Hypertension	31	22°L	184/124	2 6.5%	14 63.6%	48/56 33.8%	8 25.8%	6 27.2%	44/? ?
M. N. (F, 39)	Hypertension	40	25	173/116	8 20.0%	5 20.0%	58/34 31.9%			
M. J. L. (F, 30)	Hypertension	35	26	156/118	3 8.6%	3 11.5%	20/30 18.3%	2 5.7%	0 0.0%	6/6 4.4%
N. S. (F, 41)	Hypertension	44	25	142/100	3 6.8%	2 8.0%	30/30 24.8%	1 2.3%	6 24.0%	48/16 26.4%
M. W. (M, 26)	Hypertension	42	32	170/118	14 33.4%	15 46.9%	58/46 36.0%	7 16.7%	7 21.8%	26/22 16.7%
E. W. (F, 38)	Hypertension	40	33	186/142	2 5.0%	−1 −3.0%	54/34 26.8%	−3 −7.5%	0 0.0%	28/2 9.2%
		43	26	142/120	−15 −35.0%	−4 −15.4%	66/66 50.5%	2 4.7%	5 19.2%	28/12 15.3%
		34	30	144/116	−5 −14.7%	−8 −26.6%	78/62 53.8%	0 0.0%	−1 −3.3%	12/4 6.2%
H. F. (F, 36)	Hypertension	27 L	29 L	256/182				−8 −29.6%	0 0.0%	14/8 5.0%
S. K. (F, 44)	Hypertension anemia (Hgb. 50%)	51	25	182/120	9 17.6%	7 28.0%	46/24 23.2%	−3 −5.9%	3 12.0%	10/12 7.3%
	Same (Hgb. 90%)	35	24	210/136	3 8.6%	1 4.2%	14/26 11.5%	5 14.3%	1 4.2%	8/8 4.6%

TABLE IV—*Concluded*

SUBJECT (SEX, AGE)	DIAGNOSIS	RESTING STATE			COLD TEST			MENTAL PROBLEM		
		Blood Flow, cc./100 cc./min.		Arterial Pressure, mm. Hg	Change in Blood Flow, cc./100 cc./min. and %		Rise in Arterial Pressure, mm. Hg and %	Change in Blood Flow, cc./100 cc./min. and %		Rise in Arterial Pressure, mm. Hg and %
		Arm	Calf		Arm	Calf		Arm	Calf	
A. T. (M, 48)	Addison's disease treated (pellets)	47	33	180/112	−7 −14.9%	1 3.2%	50/56 36.3%	7 14.9%	5 15.1%	34/32 22.6%
	Same (pellets removed)	42	29	154/108	−7 −16.6%	−7 −24.1%	60/40 38.2%	3 7.2%	5 17.2%	28/6 13.0%
Average.....	Subjects with hypertension	40	29	182/130	4 9.7%	2 5.1%	43/36 26.5%	1 3.0%	2 4.7%	17/9 8.1%
			26*	177/132		8* 30.6%	40/30 21.4%		2* 7.2%	13/6 5.3%
W. C. (M, 63)	Acute glomerulonephritis	41	24	176/102	−7 −17.0%	3 12.5%	10/6 5.8%			
W. N. (M, 14)	Acute glomerulonephritis	69	48	178/114	0 0.0%	1 2.1%	6/10 5.7%	4 5.8%	−12 −25.0%	30/8 13.0%
		58	35	162/100	0 0.0%	2 5.7%	0/2 0.8%			
	Same (improving)	36	26	134/84	−3 −8.3%	0 0.0%	4/8 5.5%	0 0.0%	1 3.8%	−2/4 0.9%
Average.....	Acute glomerulonephritis	52	33	173/104	−4 −8.5%	2 8.2%	6/6 4.5%	4 5.8%	−12 −25.0%	30/8 13.0%

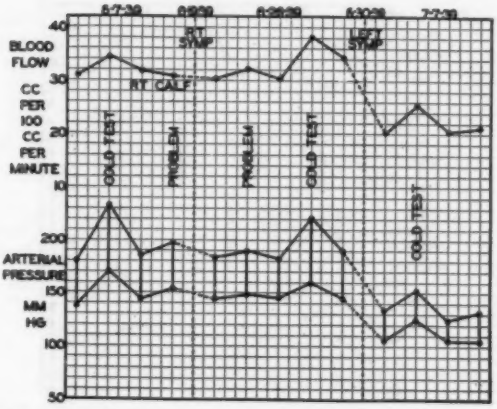

FIG. 3. Chart of arterial pressure and of reactive-hyperemia blood flow to the right calf obtained in three experiments on a patient (E. E.) with persistent essential hypertension. Splanchnic and lumbar sympathectomy performed in two stages, right on 6/19/39, left on 6/30/39. Rises of arterial pressure induced in each experiment by immersion of a hand in iced water, and in the first two experiments also by mental arithmetical problem.

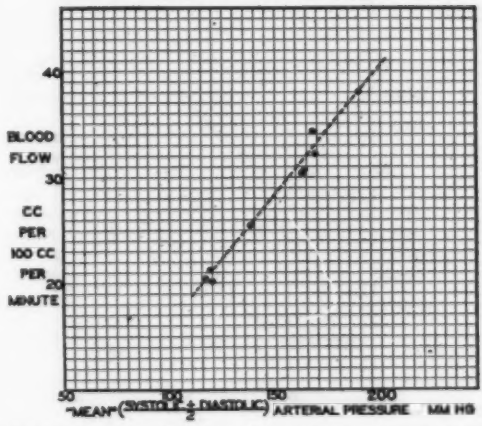

FIG. 4. Graph obtained by plotting the reactive-hyperemia blood flow to the sympathectomized right calf against the "mean" arterial pressure at the time of the flow. Data from last two experiments shown in Fig. 3.

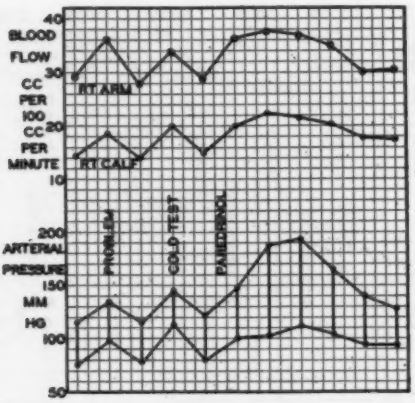

FIG. 5. Chart of arterial pressure and of reactive-hyperemia blood flow to right forearm and calf obtained in an experiment on a normal subject (R. H.). Rises of arterial pressure induced by mental arithmetical problem, by immersion of a hand in iced water, and by intramuscular administration of 25 mg. paredrinol sulfate.

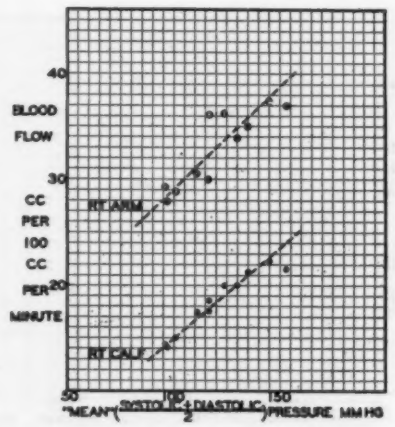

FIG. 6. Graph obtained by plotting each reactive-hyperemia blood flow to right forearm and calf against the "mean" arterial pressure at the time of the flow. Data from experiment shown in Fig. 5.

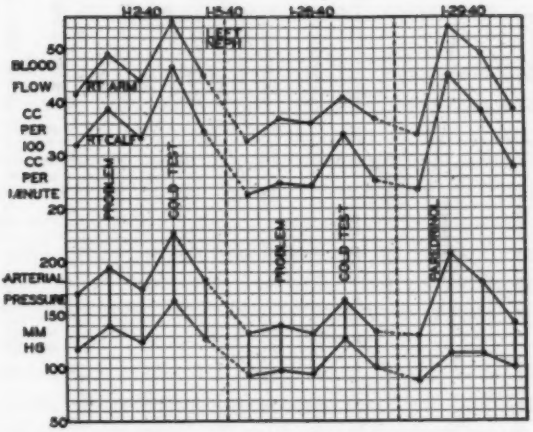

FIG. 7. Chart of arterial pressure and of reactive-hyperemia blood flow to right forearm and calf obtained in three experiments on a hypertensive patient (M. W.) with a pyelonephritic left kidney. Left nephrectomy on 1/15/40. Rises of arterial pressure induced by mental arithmetical problem, and by immersion of hand in iced water in first two experiments, and by intramuscular administration of 25 mg. paredrinol sulfate in third experiment.

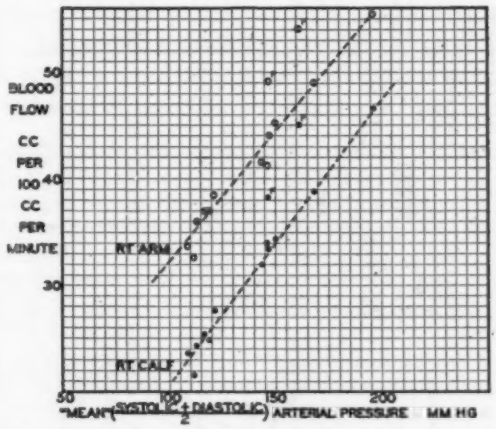

FIG. 8. Graph obtained by plotting each reactive-hyperemia blood flow to right forearm (open circles) and calf (dots) against the "mean" arterial pressure at the time of the flow. Data from the experiments shown in Fig. 7. P indicates values at height of paredrinol effect.

TABLE V

Effect of Prolonged Changes in "Basal" Arterial Pressure on Reactive-Hyperemia Blood Flow

SUBJECT	DIAGNOSIS	INITIAL DETERMINATIONS			AFTER ARTERIAL PRESSURE CHANGE			ALTERATION ACCOMPANYING ARTERIAL PRESSURE CHANGE				REMARKS
		Blood Flow, cc./100 cc./min.		Arterial Pressure	Blood Flow, cc./100 cc./min.		Arterial Pressure	Change in Blood Flow, cc./100 cc./min. (%)		Change in Arterial Pressure		
		Forearm	Calf		Forearm	Calf		Forearm	Calf	mm. Hg	Per Cent ("Mean" Pressure)	
				mm. Hg			*mm. Hg*					
M. W.	Unilateral chronic pyeloneph.	42	32	170/118	33–34	23–24	130/90	−9 (−21.4%)	−9 (−28.0%)	−40/28	(−23.6%)	Nephrectomy
E. W.	Hypertension	40	33	186/142	43	26	142/120	+3 (+7.5%)	−7 (−21.2%)	−44/22	(−20.1%)	Nephrectomy
N. S.	Hypertension	44	23–25	138/102	35	19	124/92	−9 (−20.4%)	−5 (−20.6%)	−14/10	(−10%)	Nephrectomy
E. E.	Hypertension	49	27–32	178/141	38–40	19–20	128/106	−10 (−20.4%)	−10 (−33.3%)	−50/35	(−25.0%)	Bilateral splanchnic and lumbar sympathectomy
A. T.	Addison's disease (overtreated)	47	33	180/112	42	29	154/108	−5 (−10.6%)	−4 (−12.1%)	−26/4	(−10.3%)	Pellets of desoxycorticosterone removed
W. N.	Acute nephritis	71	48	162/120	36	26	130/84	−35 (−49.2%)	−22 (−45.8%)	−32/36	(−24.1%)	Spontaneous subsidence of disease
I. H.	Addison's disease	29	19	112/84	45	30	120/88	+16 (+55.2%)	+11 (+58.0%)	+8/4	(+6.1%)	Treated with desoxycorticosterone
E. L.	Addison's disease	26	14	112/78	30	19	120/82	+4 (+15.3%)	+5 (+35.6%)	+8/4	(+6.3%)	Treated with desoxycorticosterone

desoxycorticosterone. When some of the pellets were withdrawn, both the arterial pressure and the reactive-hyperemia blood flow fell to lower levels (Table V).

General Correlation between Arterial Pressure and Reactive-Hyperemia Blood Flow. Tables III and IV record the alterations in the reactive-hyperemia blood flow in all subjects during induced changes in arterial pressure. In sympathectomized limbs the reactive-hyperemia blood flow always varied directly with the arterial pressure, even during severe sensory stimuli. In normally innervated limbs, especially of hypertensive subjects (note B. B., S. G., T. R. and E. W.), the reactive-hyperemia blood flow did not always vary directly with the arterial pressure, particularly during severe sensory stimuli. This was attributed to local sympathetic vasoconstrictor activity. A previous study (7) has shown that sympathetic vasoconstrictor activity during severe sensory stimuli in certain individuals may significantly alter the reactive-hyperemia blood flow. In the majority of instances, however, the reactive-hyperemia blood flow even in the normally innervated limbs varied directly with the arterial pressure. Observations showing a direct correlation between arterial pressure and reactive-hyperemia blood flow are summarized graphically in Figures 9 and 10. The results selected for plotting in these figures were obtained in cases in which the induced alterations in mean arterial pressure were at least as great as 20 mm. Hg.

Forearm: In 10 subjects when the mean arterial pressure was raised from normal by at least 20 mm. Hg, the reactive-hyperemia blood flow averaged 38 cc./100 cc./min. (limits 29 cc. to 50 cc./100 cc./min.). In 4 hypertensive subjects when the mean arterial pressure was lowered by at least 20 mm. Hg, the reactive-hyperemia blood flow averaged 38 cc./100 cc./min. (limits 19 cc. to 43 cc./100 cc./min.). In 13 hypertensive subjects when the mean arterial pressure was raised by at least 20 mm. Hg, the reactive-hyperemia blood flow averaged 47 cc./100 cc./min. (limits 26 cc. to 72 cc./100 cc./min.).

Calf: In 8 subjects when the mean arterial pressure was raised from normal by at least 20 mm. Hg, the reactive-hyperemia blood flow averaged 29 cc./100 cc./min. (limits 19 cc. to 44 cc./100 cc./min.). In 4 hypertensive subjects when the mean arterial pressure was lowered by at least 20 mm. Hg, the reactive-hyperemia blood flow averaged 22 cc./100 cc./min. (limits 19 cc. to 26 cc./100 cc./min.). In 11 hypertensive subjects when the blood pressure was raised by at least 20 mm. Hg, the reactive-hyperemia blood flow averaged 32 cc./100 cc./min. (limits 14 cc. to 47 cc./100 cc./min.).

In all of these observations it may be noted that the alterations in blood flow induced by raising or lowering the arterial pressure, while

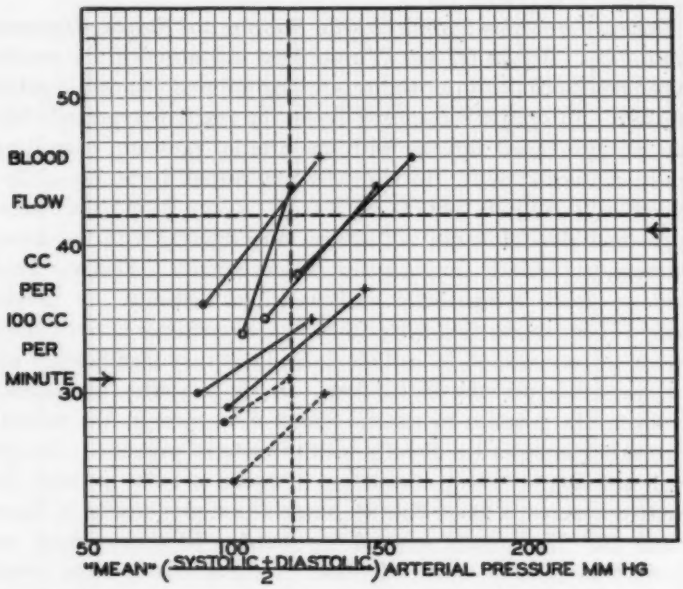

FIG. 9. Graph showing typical changes in reactive-hyperemia blood flow to forearm plotted against induced changes in mean arterial pressure in normal and hypertensive subjects. Each line represents changes in blood flow and arterial pressure induced by a single procedure. Continuous lines, normally innervated limbs; interrupted lines, sympathectomized limbs. Solid dots indicate original arterial pressure and blood flow. Cross indicates arterial pressure and blood flow during a pressor procedure; open circle, values during a depressor procedure. For sympathectomized arms pressor procedure was immersion of the opposite hand in iced water. For normally innervated arms pressor procedure was intramuscular injection of 25 mg. paredrinol sulfate. Depressor procedure was removal of a diseased kidney. In this and the following charts, vertical interrupted line indicates upper limit of normal mean arterial pressure. Horizontal interrupted lines indicate upper and lower limits of reactive hyperemia blood flow observed in subjects with normal arterial pressure. Arrow on left indicates average normal blood flow; arrow on right, average blood flow in hypertensive subjects.

definite for a given individual, occurred usually within the rather wide normal range. In only an occasional subject was the blood flow so

altered by changes in arterial pressure that it lay beyond the observed limits of normal. With alterations in mean arterial pressure greater than 20 mm. Hg the associated changes in blood flow in the forearm averaged only 6 cc./100 cc./min., while those in the calf averaged only

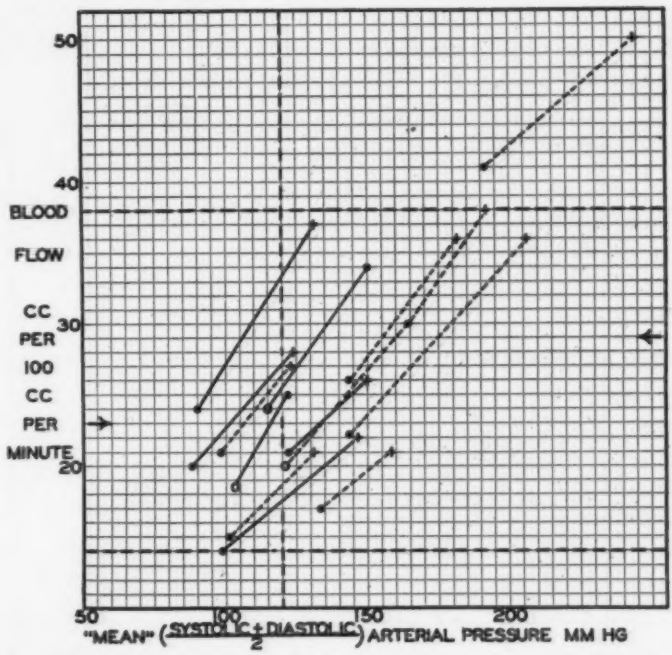

FIG. 10. Graph showing typical changes in reactive-hyperemia blood flow to calf plotted against induced changes in mean arterial pressure in normal and hypertensive subjects. Symbols as in Figure 9. For sympathectomized calves pressor procedure was immersion of a hand in iced water. For normally innervated calves pressor procedure was intramuscular injection of 25 mg. paredrinol sulfate. For sympathectomized calves depressor procedure was completion of bilateral splanchnic and lumbar sympathectomy. For normally innervated calves depressor procedure was removal of diseased kidney.

5 cc./100 cc./min. Changes of this order of magnitude have been observed in the "spontaneous" variations in reactive-hyperemia blood flow which occur in both the forearm and calf (7). Such variations, however, are usually observed only when the determinations of blood

flow are separated by intervals of several weeks or months, and it is believed that they have not materially affected the results obtained in the present study.

Comparison of Blood Flow in a Group of Hypertensive and a Group of Normal Subjects

Typical reactive-hyperemia blood flows observed in the forearms and calves of 16 patients with hypertension, are shown in Table I.

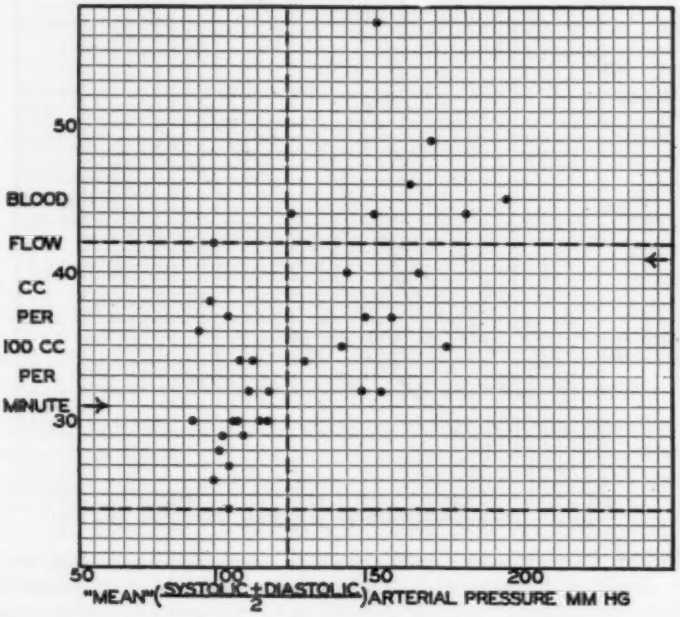

FIG. 11. Scatter-chart of reactive hyperemia blood flows to forearms of all subjects plotted against mean arterial pressures. Each dot represents the blood flow and simultaneously determined arterial pressure in a single subject.

Similar figures for 22 subjects with normal arterial pressure are given in Table II. The arterial pressures recorded in these tables are intended to indicate the full range of pressures obtained during the determinations of blood flow. The correlation, in these same subjects, between reactive-hyperemia blood flow and simultaneously determined arterial pressure is shown in two scatter-charts (Figs. 11 and 12).

In both the forearm and the calf, particularly in the former, there is a tendency toward a greater blood flow in the hypertensive subjects. This is reflected in the averages indicated by the arrows at the margins of the scatter charts. In the forearm (Fig. 11), the average reactive-hyperemia blood flow was 31 cc./100 cc./min. in 20 subjects with normal arterial pressure, and 42 cc./100 cc./min. in 16 subjects with essential hypertension. In the calf (Fig. 12), the average reactive-

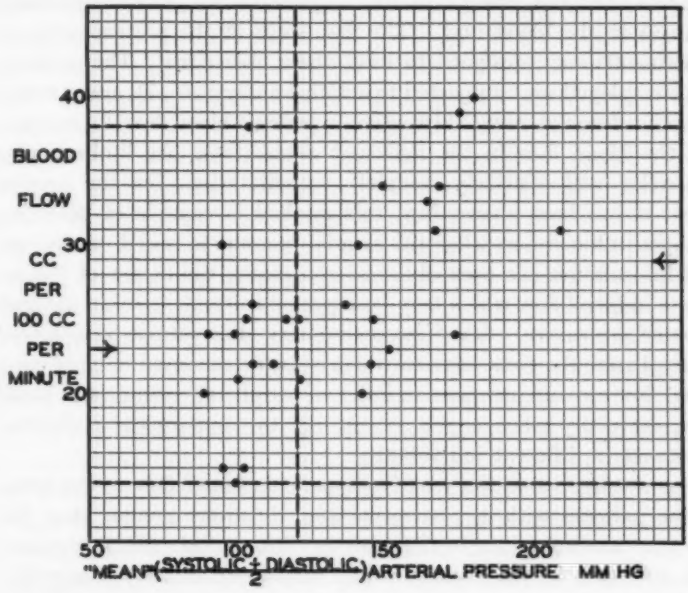

FIG. 12. Scatter-chart of reactive hyperemia blood flows to calves of all subjects plotted against mean arterial pressures. Symbols as in Figure 11.

hyperemia blood flow was 23 cc./100 cc./min. in 14 subjects with normal arterial pressure, and 29 cc./100 cc./min. in 16 subjects with essential hypertension. However, in both the forearm and the calf there is much overlapping of the values for the hypertensive and the normal groups.

DISCUSSION

The present study does not support the conclusions of previous investigators (3, 4, 5), that in the limbs of hypertensive subjects there

is an increased resistance to blood flow which cannot be reduced to normal by physiologic methods of vasodilatation. On the other hand, this study does not offer conclusive proof to the contrary.

The earlier investigations are open to at least two types of criticism: (a) that the methods employed for producing vasodilatation failed by a considerable margin to bring about full dilatation; and (b) that no evidence was offered to show that when the peripheral resistance remains unaltered, changes in arterial pressure bring about significant changes in the blood flow. The first steps in the present series of experiments were designed to meet these objections. The methods to be employed were subjected to detailed analysis (6, 7), and a standard procedure was adopted (reactive-hyperemia blood flow) for measuring the blood flow in the muscular segments of the limbs during controlled and relatively complete vasodilatation. In the present paper it has been shown that this method is capable of detecting changes in blood flow when the arterial pressure is raised or lowered; and information has been obtained concerning the extent of the increase in blood flow which may be expected to result from an increase in arterial pressure. All of the preliminary observations have served to emphasize the great caution which must be exercised in employing blood flow measurements as an index of peripheral resistance to blood flow, especially when one is attempting to compare the peripheral resistance in different individuals.

The average values for reactive-hyperemia blood flow to the limbs of the patients with hypertension were definitely greater than the average values obtained in the subjects with normal arterial pressure. The difference in the average values was approximately that which might have been expected to result from the difference in arterial pressure alone. However, one is not warranted in concluding from this that during controlled vasodilatation the peripheral resistance in the hypertensive subjects was approximately the same as that in the normal subjects. There are several reasons for avoiding such a conclusion: (a) The figures for reactive hyperemia blood flow in normal subjects cover a relatively wide range which overlaps the range of figures obtained in hypertensive subjects. (b) Owing chiefly to the overlapping of figures, the observations are not sufficiently numerous for statistical analysis. (c) In individual subjects the alterations

in reactive hyperemia blood flow associated with even considerable changes in arterial pressure, while significant for the individual concerned, are small in comparison with the wide normal range. Hence, for the individual patient with hypertension, no conclusion can be drawn as to whether his observed blood flow is above his own "normal" level, unless, as occasionally happens, the values are clearly beyond the normal range. These same considerations must be borne in mind in interpreting the results reported by previous investigators.

Although the observations upon the hypertensive patients, as a group, must be considered inconclusive, the observations upon certain of the individual patients are perhaps of greater significance. This is particularly true in the cases in which marked reductions in the basal level of arterial pressure followed appropriate operative procedures. In all of these cases, the fall in arterial pressure was accompanied by an immediate decrease in reactive-hyperemia blood flow, which was in accord with the direct relationship observed preoperatively between the arterial pressure and the blood flow. This suggests that the fall in pressure was not due to a decrease in the peripheral resistance in the muscular segments of the extremities, in so far as this could be estimated by blood flow determinations made during vasodilatation. It is not known whether the postoperative fall in arterial pressure was due to a decrease in resistance in other vascular areas. At least it can be stated that the fall in pressure was not the result of a universal increase in the ability of the vascular system to dilate under the conditions employed in these experiments. It should also be emphasized that while in these patients the blood flow decreased when the arterial pressure was lowered, it did not fall below the normal range. Thus, no apparent ischemia of the limbs resulted from the reduction in arterial pressure.

In the hypertensive patients subjected to splanchnic and lumbar sympathectomy, there was never an increase in blood flow to the sympathectomized calf. The reactive-hyperemia blood flow to the calf varied directly with changes in arterial pressure. The blood flow to the calf in the natural resting state (i.e., without reactive hyperemia) with the subject comfortably warm, was reduced following sympathectomy as it is in subjects with normal arterial pressure (6). This was true whether or not the basal arterial pressure was altered by the

operation. Hence, any lowering of arterial pressure which occurred could not be attributed to a release of resistance to blood flow in the muscular segments of the sympathectomized limbs. Here again information is lacking concerning the effect of the sympathectomy upon other portions of the body supplied by the nerves which were resected.

Certain incomplete observations suggest that in some patients a structural, or a slowly reversible, functional, type of resistance may develop in the limbs after hypertension has been present for some time, and may slowly regress after the arterial pressure has been reduced for a long period. For example, one patient (H. F.) with an arterial pressure of 228/150 and a reactive-hyperemia blood flow of 47 cc./100 cc./min. in the forearm when she was in relatively good physical condition, returned 6 months later in a terminal "malignant" phase. The arterial pressure was then 256/182 but the reactive-hyperemia blood flow to the forearm was only 27 cc./100 cc./min. Three hypertensive patients, one (E. E.) after splanchnic and lumbar sympathectomy, and the other two (E. W. and M. W.) after unilateral nephrectomy, had sustained reductions of arterial pressure and proportional decreases in reactive-hyperemia blood flow to the forearm and calf. When retested 4 to 6 months later, the arterial pressure in each case had remained at the lower level, but the reactive-hyperemia blood flow had increased to almost the preoperative value.

Such measurements, made in only a few patients, and scattered over a period of months, are of questionable significance unless confirmed by additional studies. Attention has already been directed to the unexplained variations in blood flow which may be observed, especially when the measurements are separated by long intervals of time. In interpreting the results mentioned above, one must take into account not only these "spontaneous" variations but also other factors which may come into play in patients whose state of health is changing.

It has been noted earlier that the hypertensive patients selected for this study present the clinical picture of essential hypertension. Yet the group contains patients of various ages and at various stages in the evolution of hypertensive disease; and it may be made up of individuals with several distinct types of hypertension. At the present time

too little is known about the etiology of essential hypertension to permit one to look upon it as a disease entity in which the findings in a group of cases can be averaged and treated statistically.

The blood flow studies seem to indicate that there is a form of hypertension, or a stage in the development of hypertensive disease, in which the vessels of the muscular segments of the limbs are not involved in an irreversible type of vasoconstriction. The observations are compatible with the view that the irreversible or structural narrowing of the vessels in the muscular segments is a response to, and not an essential part of the cause of the hypertension.

SUMMARY AND CONCLUSIONS

1. Within the range of the arterial pressures encountered in human subjects there is a direct relationship between arterial pressure and blood flow to the sympathectomized forearm or calf in which vasodilatation has been induced by a standard method (reactive-hyperemia). There is also a direct relationship between arterial pressure and blood flow to the normally innervated forearm and calf during vasodilatation similarly induced, except after severe sensory stimuli, when, in certain subjects, local vasoconstrictor activity may disturb this relationship.

2. This relationship holds both in normal and hypertensive subjects.

3. The alteration in reactive-hyperemia blood flow, associated with even a great change in arterial pressure, while definite for a given subject, often is not great enough to result in a blood flow which is clearly beyond the limits of normal.

4. In subjects with normal arterial pressure, the values for reactive-hyperemia blood flow cover a wide range which overlaps the range of values obtained in hypertensive subjects.

5. When the same conditions of vasodilatation are imposed, there is no significant difference between the blood flow to the forearm and calf in certain normal subjects in whom rises in arterial pressure have been induced, and the blood flow in certain hypertensive patients. There is no difference between the blood flow to the forearm and calf in certain hypertensive patients whose arterial pressures have been lowered, and the blood flow in normal subjects with the same arterial pressures.

6. While not sufficient for statistical analysis, our data are consistent with the view that in certain hypertensive patients the blood flow to the forearm and calf during controlled vasodilatation is greater than normal for those subjects.

7. The present study has raised doubts concerning the validity of the conclusions of previous investigators, that in patients with essential hypertension the vessels of the muscular segments of the limbs are involved in a generalized increased peripheral resistance which cannot be released by physiologic vasodilatation.

This investigation was conducted with the technical assistance of Miss Sara B. Merritt, B.S.

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BIBLIOGRAPHY

1. Weiss, S., and Ellis, L. B., The quantitative aspects and dynamics of the circulatory mechanism in arterial hypertension. *Am. Heart J.*, 1930, **5**, 448.
2. Lequime, J., Le debit cardiaque au cours de l'hypertension essentielle. *Compt. rend. Soc. de biol.*, 1937, **126**, 76.
3. Prinzmetal, M., and Wilson, C., The nature of the peripheral resistance in arterial hypertension with special reference to the vasomotor system. *J. Clin. Invest.*, 1936, **15**, 63.
4. Pickering, G. W., The peripheral resistance in persistent arterial hypertension. *Clin. Sc.*, 1936, **2**, 209.
5. Stead, E. A., Jr., and Kunkel, P., Nature of peripheral resistance in arterial hypertension. *J. Clin. Invest.*, 1940, **19**, 25.
6. Wilkins, R. W., and Eichna, L. W., Blood flow to the forearm and calf. I. Vasomotor reactions: rôle of the sympathetic nervous system. *Bull. Johns Hopkins Hosp.*, 1941, **68**, 425.
7. Eichna, L. W., and Wilkins, R. W., Blood flow to the forearm and calf. II. Reactive hyperemia: factors influencing the blood flow to limbs during vasodilatation following ischemia. *Bull. Johns Hopkins Hosp.*, 1941, **68**, 450.
8. Hines, E. A., and Brown, G. E., A standard test for measuring the variability of blood pressure: its significance as an index of the prehypertensive state. *Ann. Int. Med.*, 1933, **7**, 209.
9. Alam, M., and Smirk, F. H., Observations upon a blood pressure raising reflex arising from the voluntary muscles. *J. Physiol.*, 1937, **89**, 372.

10. Stead, E. A., Jr., and Kunkel, P., Mechanism of the arterial hypertension induced by paredrinol (α-N-dimethyl-p-hydroxyphenethylamine). *J. Clin. Invest.*, 1939, **18**, 439.
11. Pickering, G. W., Observations on the mechanism of arterial hypertension in acute nephritis. *Clin. Sc.*, 1936, **2**, 363.
12. Arnott, W. M., and Matthew, G. D., The nature of the arteriolar hypertonicity in acute glomerulo-nephritis. *Quart. J. Med.*, 1939, **8**, 353.

BLOOD FLOW TO THE FOREARM AND CALF

IV. Thyroid Activity: Observations on the Relation of Blood Flow to Basal Metabolic Rate[1]

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Hyperthyroidism is known to be associated with an increased cardiac output (1, 2), a low diastolic arterial pressure and an increased arterial pulse pressure, a decreased circulation time (3, 4) and an increased blood flow in the skin (5). The increased cardiac output, the type of arterial pressure and the rapid velocity of blood flow all indicate a reduction in the total "vascular" resistance to a level below normal. The increased blood flow in the skin might be due merely to the need for greater radiation of heat at the higher metabolic rate. Whether there is also an increased blood flow to the muscular segments of the forearm and calf, regions less concerned than the skin with the regulation of body temperature, is not known. In the course of other studies (6, 7, 8) it was possible to make measurements of blood flow to the forearm and calf of a few patients with disturbed thyroid activity, both before and after therapy. It seemed worth while to record these observations.

METHODS

By a method previously described (6), simultaneous plethysmographic determinations were made of the blood flow to muscular segments of the forearm and calf. Measurements were made both in the resting state and during the earliest part of the reactive hyperemia following a five-minute period of arterial occlusion (7). The patients lay supine for one hour before determinations were begun. The limbs were at heart level. Reflex vasodilatation was induced by warming the body. The temperature of the water in the plethysmograph was constant at 32°C.; that of the room was usually 20°C. Arterial pressure was

[1] Supported by a grant from The Commonwealth Fund for the study of essential hypertension.

determined by the auscultatory method, using a mercury manometer. The vasomotor stimuli of the cold test and mental problem were applied in a manner already described (6). The basal metabolic rate was determined within one day of the blood flow measurements.

Studies were made on 7 patients; 5 with typical hyperthyroidism, 1 with adult hypothyroidism, and 1 with a peculiar muscular hypertrophy[2] accompanied by an abnormally low basal metabolic rate. The routine therapeutic administration of phenobarbital was not interrupted, but no additional sedative medication was given either immediately before or during the blood flow determinations. The patients with hyperthyroidism were prepared for subtotal thyroidectomy by the administration of iodide. Blood flow measurements were made upon the same segments of the same limbs both pre- and postoperatively.

RESULTS

Blood Flow to the Resting Forearm and Calf. During active hyperthyroidism and before the institution of iodide therapy, the blood flow to the resting limbs was distinctly greater than that in normal subjects. In 5 patients (Table I) the blood flow to the resting forearm varied from 5.5 to 16.5 cc./100 cc./min., averaging 10.2 cc./100 cc./min.; and that to the resting calf varied from 5.75 to 14.3 cc./100 cc./min., averaging 8.6 cc./100 cc./min. This contrasts markedly with the previously determined normal values (6): 2.3 to 7 cc./100 cc./min. (average 4.1 cc./100 cc./min.) to the resting forearm, and 1.4 to 6.5 cc./100 cc./min. (average 3.7 cc./100 cc./min.) to the resting calf.

The effect of vasomotor stimuli upon these more rapid blood flows was generally the same as upon the blood flows in normal subjects. The strong vasoconstricting stimulus of the cold test reduced the blood flow to both the forearm and calf, although at times, only slightly so. The vasodilator stimulus of solving an arithmetical problem induced slight increases in blood flow but occasionally had no effect whatever.

The preoperative administration of iodides lowered the basal metabolic rate but this reduction in metabolism was not always associated with a decrease in the resting blood flow (Table I). When the basal metabolic rate of one patient (C. S.) was lowered from +78 per cent to +31 per cent the blood flow to the forearm decreased sig-

[2] This case recently has been described in detail: Hesser, F. H., Hypertrophia Musculorum Vera (Dystrophia Musculorum Hyperplastica) Associated with Hypothyroidism: A case study. *Bull. Johns Hopkins Hospital*, 1940, **66**, 353.

TABLE I

Relation of Blood Flow to Basal Metabolic Rate

PATIENT (SEX, AGE)	DATE	BLOOD FLOW, CC./100 CC./MIN.				B.M.R.	ARTERIAL PRESSURE, MM. Hg		REMARKS
		Resting State		Reactive Hyperemia			During Resting State	During Reactive-Hyperemia Blood Flow	
		Forearm	Calf	Forearm	Calf				
Hyperthyroidism									
						per cent			
C. S. (M, 45)	3/15/40	16.4	14.3	52	34	+78	138/48	148/74	
	4/ 1/40	6.4	6.25	38	26	+31	126/58	118/60	After Lugol's solution for 7 days
	4/12/40	1.7	2.4	38	22	+3	118/70	122/70	6 days after subtotal thyroidectomy
	5/29/40	1.6	1.7	28	17	−24	112/80	118/86	7 weeks postoperative
D. H. (F, 18)	4/26/40	12.8	9.6	49	26	+71	136/62	138/58	
	5/10/40	12.0	5.9	55	25	+77	144/50	144/64	After Theelin 1 cc. daily for 10 days
	6/ 7/40	13.9	9.75	53	28	+43	136/58	132/66	After Lugol's solution for 14 days
	7/ 1/40	6.9	2.6	36	18	−5	126/74	116/72	12 days after subtotal thyroidectomy
J. F. (M, 21)	6/14/40	5.8	7.1	43	38	+64	122/68	144/84	
	6/28/40	4.0	5.0	36	32	+32	142/84	136/80	After Lugol's solution for 12 days
	7/ 8/40	3.4	1.8	41	31	−4	126/84	126/80	7 days after subtotal thyroidectomy
H. J. (M, 47)	4/24/40	5.5	6.3	34	30	+80	144/94	152/102	
	5/17/40	4.8	2.8	40	29	+17	144/102	152/112	9 days after subtotal thyroidectomy
	7/25/40	4.2	3.6	38	28	−3	130/96	156/110	10 weeks postoperative
L. M. (F, 45)	4/17/40	10.6	5.8	45	28	+64	194/104	190/108	
	6/ 5/40	10.3	4.6	44	27	+44	174/90	184/92	26 days after subtotal thyroidectomy
Average, untreated hyperthyroidism		10.2	8.6	45	31				

TABLE I—*Concluded*

PATIENT (SEX, AGE)	DATE	BLOOD FLOW, CC./100 CC./MIN.				B.M.R.	ARTERIAL PRESSURE, MM. Hg		REMARKS
		Resting State		Reactive Hyperemia			During Resting State	During Reactive-Hyperemia Blood Flow	
		Forearm	Calf	Forearm	Calf				
Hypothyroidism									
						per cent			
B. C. (F, 40)	5/27/40	3.4	2.25	18	14	−31	108/78	100/72	
L. F. (F, 30)	10/13/39	2.0	1.2	23	9	−28	102/80	94/72	Patient with muscular hypertrophy
	11/15/39	7.0	4.5	45	28	+10	102/68	108/72	After thyroid substance 0.1-0.2 gram daily for 25 days
Average, untreated hypothyroidism		2.7	1.7	20	12				

nificantly from 16 to 6 cc./100 cc./min. and that to the calf from 14 to 6 cc./100 cc./min. (Fig. 1). But in another patient (D. H.), a reduction in the basal metabolic rate from +71 per cent to +43 per cent was accompanied by no change in blood flow to the forearm (12.8 and 13.9 cc./100 cc./min., respectively) nor to the calf (9.6 and 9.75 cc./100 cc./min., respectively). Following subtotal thyroidectomy, the basal metabolic rate returned to normal in four patients. In each, there was a decrease in the resting blood flows to normal values (Table I, Fig. 1). In the fifth patient, the basal metabolic rate remained elevated (+44 per cent) after thyroidectomy and the blood flow did not decrease.

In some patients, when the basal metabolic rate was lowered and the blood flow decreased, the same vasomotor stimuli induced greater alterations in blood flow than previously. The cold test caused greater decreases, and the mental problem, greater increases in blood flow than when the basal metabolic rate and resting blood flow had been elevated.

The two patients with abnormally low basal metabolic rates had resting blood flows within the normal range. To the forearm the blood flow in one subject was 3.4 cc./100 cc./min., in the other 2.0 cc./100 cc./min. To the calf the resting blood flows in the same subjects were 2.25 cc./100 cc./min. and 1.2 cc./100 cc./min., respectively. During the cold test the blood flow to both the forearm and calf was markedly reduced in each subject. The mental problem induced considerable increases in blood flow to both the upper and lower extremities in each patient.

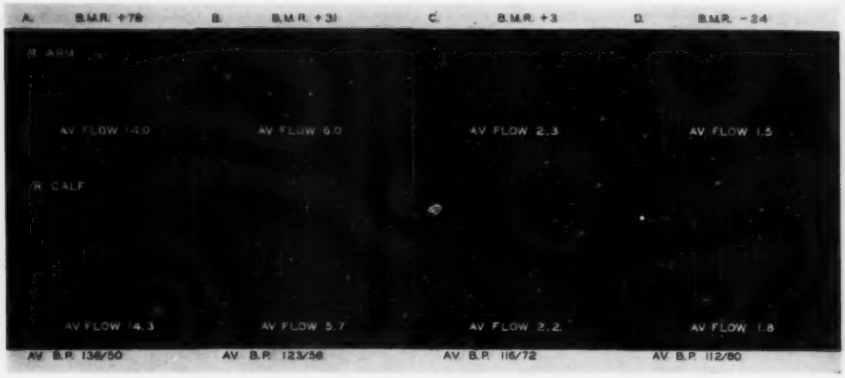

FIG. 1. Plethysmographic tracings of blood flow to the resting right forearm and calf of a patient (C. S.) with hyperthyroidism. Each group of three blood flow determinations represents a different experiment. A. Before treatment. B. After treatment for one week with Lugol's solution. C. One week after subtotal thyroidectomy. D. Seven weeks after subtotal thyroidectomy. The figures above each group give the basal metabolic rate in per cent; those below, the average arterial pressure in mm. Hg. The white figures below each set of blood flows give the calculated average blood flow in cc./100 cc./min. Time, seconds.

The patient with the peculiar muscular hypertrophy had a blood flow of 2.0 cc./100 cc./min. to the forearm and of 1.2 cc./100 cc./min. to the calf when the basal metabolic rate was −28 per cent. Treatment with thyroid substance (0.1 to 0.2 gram by mouth daily for 25 days) raised the basal metabolic rate to +10 per cent, at which time the blood flow to the forearm was 7.0 cc./100 cc./min. and that to the

calf 4.5 cc./100 cc./min., increases of 250 per cent and 275 per cent, respectively.

Blood Flow During Reactive Hyperemia of Forearm and Calf. In the untreated phase of hyperthyroidism, the reactive-hyperemia blood flow to the forearm of these five patients varied from 34 to 52 cc./100 cc./min. (Table I). In four of the five patients the blood flow to the forearm exceeded the highest normal value of 42 cc./100 cc./min. The average value for the entire hyperthyroid group was 45 cc./100 cc./min., definitely greater than the average normal value of 31 cc./100 cc./min. (7).

In the same phase of the disease, the reactive-hyperemia blood flow to the calf varied from 26 to 38 cc./100 cc./min. (Table I). Although these values all fell within the limits of normal, they occupied the upper range of normal. Furthermore, the average value of 31 cc./100 cc./min. for the hyperthyroid group distinctly exceeded the normal average value of 23 cc./100 cc./min. (7). In neither the forearm nor the calf was there a direct correlation between the reactive hyperemia blood flow and the basal metabolic rate.

In spite of the high initial level of reactive-hyperemia blood flow in these patients, the augmentation previously described (7) occurred with successive determinations until three or four had been made, when the blood flow became stabilized. The degree of this augmentation tended to be greater than that for normal subjects. In the forearms of four patients, the increase in blood flow between the first and fourth determinations amounted to 10 to 17 cc./100 cc./min. (30.4 per cent to 48.5 per cent). In the fifth patient the increase was but 1 cc./100 cc./min. (3.1 per cent). When the blood flow to the forearm was redetermined, after the basal metabolic rate had returned to normal, the augmentation with successive determinations was more like that seen in normal subjects: 3 to 6 cc./100 cc./min. (7.9 per cent to 27.2 per cent). The augmentation of reactive-hyperemia blood flow to the calf was not so great, 2 to 9 cc./100 cc./min. (7.2 per cent to 36.8 per cent) when the basal metabolic rate was elevated and 2 to 5 cc./100 cc./min. (8 per cent to 21.4 per cent) when the metabolic rate had returned to normal. The tendency for the arterial pressure to rise as the experiment progressed may have been a factor in the hyperthyroid state, which accentuated the augmentation phenom-

enon. In these patients even slight rises in arterial pressure appeared to invoke considerable increases in blood flow.

Prolonging to 10 or 15 minutes the duration of the ischemic period usually increased the resultant reactive-hyperemia blood flow to both the forearm and calf. However, these longer periods of arterial occlusion were also associated with rises in arterial pressure. This made it difficult to judge whether the increases in blood flow after the longer periods of ischemia were due to greater vasodilatation in the part or merely to the higher arterial pressure.

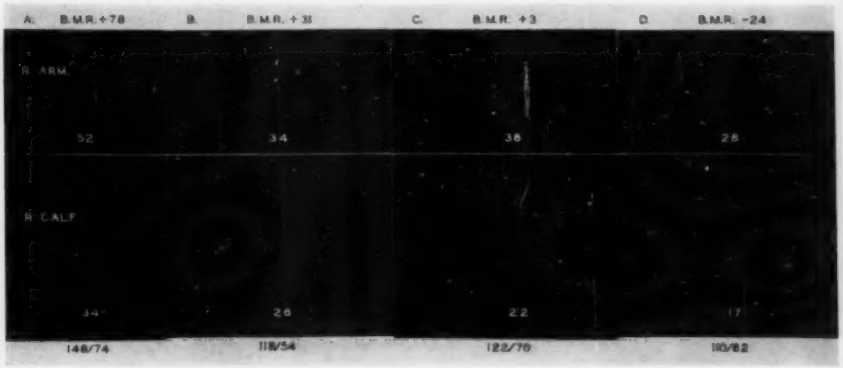

FIG. 2. Plethysmographic tracings of the reactive-hyperemia blood flow to the right forearm and calf of a patient (C. S.) with hyperthyroidism. Each blood flow represents a different experiment. A. Before treatment. B. After treatment for one week with Lugol's solution. C. One week after subtotal thyroidectomy. D. Seven weeks after subtotal thyroidectomy. Figures above tracings give the basal metabolic rate in per cent; those below, the arterial pressure in mm. Hg. White figure below each tracing gives the blood flow in cc./100 cc./min. Time, quarter-seconds, and seconds.

In three of the four patients whose basal metabolic rates returned to normal following iodide medication and subsequent subtotal thyroidectomy, there was an associated decrease in reactive-hyperemia blood flow to the calf (Fig. 2, Table I). In two of these patients there was also a decrease in the blood flow to the forearm. In the fourth patient, there was no decrease in blood flow to either the forearm or the calf. In one patient (L. M.), whose basal metabolic rate fell only

from +64 per cent to +44 per cent, the blood flow to both the forearm and calf remained unchanged. The reactive-hyperemia blood flow could not be correlated directly with the changes in metabolic rate, either during the preoperative period or after thyroidectomy. The general trend, however, was for the two determinations to vary in the same direction.

In the two patients with abnormally low basal metabolic rates, the reactive-hyperemia blood flow to the limbs was below or at the lower limit of normal. One patient with a basal metabolic rate of −31 per cent had a blood flow of 18 cc./100 cc./min. to the forearm and of 14 cc./100 cc./min. to the calf. In the patient with the peculiar muscular hypertrophy, when the basal metabolic rate was −28 per cent, the reactive-hyperemia blood flow to the forearm was 23 cc./100 cc./min. and that to the calf but 9 cc./100 cc./min. After the administration of thyroid substance (0.1 to 0.2 gram by mouth daily for 25 days) the basal metabolic rate rose to +10 per cent and the blood flow to the forearm increased twofold (to 45 cc./100 cc./min.), while that to the calf increased threefold (to 28 cc./100 cc./min.).

DISCUSSION

In five patients with active untreated hyperthyroidism the blood flow to the forearm and calf tended to be increased not only in the resting state but also during reactive hyperemia. Since, in three of the five subjects, these increased blood flows were associated with normal mean arterial pressures, the resistance of the vascular beds of the muscular segments of the forearm and calf was probably reduced below the normal level, both in the resting state and during strong physiologic vasodilatation.

The failure to demonstrate in these patients a consistent correlation between blood flow and basal metabolic rate suggests that the blood flow may be dependent not upon the actual metabolism of the tissue but upon some other factor secondarily induced by hyperthyroidism. In guinea pigs, the administration of thyroxin has been reported to bring about an increase in the number of capillaries in both heart and skeletal muscle (9). This increased vascularization of muscle was attributed to the formation of new capillaries rather than to the opening up of a larger number of already existing capillaries. If

similar changes occur in man during hyperthyroidism, and lag behind the more rapidly occurring changes in metabolic rate, they would explain both the increased blood flow in hyperthyroidism and its failure to vary consistently with the basal metabolic rate. Furthermore, one could then attribute the decreased vascular resistance in hyperthyroidism not merely to the vasodilatation of a fixed existing vascular bed, but also to the development of new vascular channels. Whether this explanation is correct, the present study does not indicate.

Hyperthyroidism was associated with hypertension in two patients. It is of interest that in these two patients the values obtained for the blood flow to the limbs, both resting and under vasodilatation, were similar to the figures obtained in the three patients whose arterial pressure was normal. It may be significant that in the two hypertensive patients the reactive-hyperemia blood flow showed no decrease with the fall in basal metabolic rate following subtotal thyroidectomy.

Only two patients with hypothyroidism were studied, and one of these presented a peculiar muscular hypertrophy which rendered her limbs distinctly unusual for study of the circulation. Nevertheless, the data obtained in these two patients suggest that in hypothyroidism the circulation to muscular segments of the limbs is affected in a direction opposite to that found in the hyperthyroid group.

SUMMARY

1. In 5 patients with active hyperthyroidism the blood flow to the muscular segments of extremities tended to be greater than that found in normal subjects. This was true of extremities both at rest and during the vasodilatation following ischemia.

2. Vasomotor stimuli induced in these hyperthyroid patients changes in blood flow similar to those found in normal subjects.

3. The blood flow tended to decrease as the hyperthyroidism was relieved and the basal metabolic rate fell.

4. In 2 patients with hypothyroidism, the blood flow to muscular segments of the extremities both at rest and during vasodilatation was decreased to or below the lower limit of normal.

This investigation was conducted with the technical assistance of Miss Sara B. Merritt, B.S.

The authors gratefully acknowledge the helpful advice and criticism of Dr. James Bordley, III.

BIBLIOGRAPHY

1. GROLLMAN, A., *The cardiac output of man in health and disease.* Charles C. Thomas, Springfield, 1932, p. 242.
2. LEQUIME, J., Modifications du débit cardiaque dans l'hyperthyroidie. *Compt. rend. Soc. de Biol.*, 1937, **124**, 862.
3. BLUMGART, H. L., The velocity of blood flow in health and disease. The velocity of blood flow in man and its relation to other measurements of the circulation. *Medicine*, 1931, **10**, 1.
4. KVALE, W. F., AND ALLEN, E. V., The rate of the circulation in the arteries and veins of man. I. Studies of normal subjects and of those with occlusive arterial disease and hyperthyroidism. *Amer. Heart J.*, 1939, **18**, 519.
5. STEWART, H. J., AND EVANS, W. F., The peripheral blood flow in hyperthyroidism. *J. Clin. Invest.* 1940, **19**, 779.
6. WILKINS, R. W., AND EICHNA, L. W., Blood flow to the forearm and calf. I. Vasomotor reactions: rôle of the sympathetic nervous system. *Bull. Johns Hopkins Hosp.*, 1941, **68**, 425.
7. EICHNA, L. W., AND WILKINS, R. W., Blood flow to the forearm and calf. II. Reactive hyperemia: factors influencing the blood flow to limbs during vasodilatation following ischemia. *Bull. Johns Hopkins Hosp.*, 1941, **68**, 450.
8. WILKINS, R. W., AND EICHNA, L. W., Blood flow to the forearm and calf. III. The effect of changes in arterial pressure on the blood flow to limbs under controlled vasodilatation in normal and hypertensive subjects. *Bull. Johns Hopkins Hosp.*, 1941, **68**, 477.
9. ERIKSSON, N-O., AND PETRÉN, T., Untersuchungen über die Blutversorgung von Herz- und Skelettmuskeln bei Hyper- und Hypothyreosezuständen. *Gegenbaurs Morphol. Jahrb.*, 1937, **80**, 445.

A RAPID METHOD FOR THE DETERMINATION OF DIODRAST-IODINE IN BLOOD AND URINE[1]

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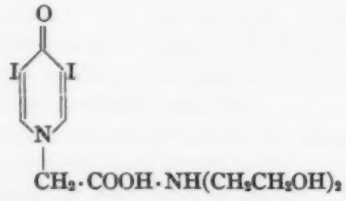
The use of the clearance of *Diodrast* by the kidney as a measure of *effective renal blood flow* in man has been developed by Smith and his co-workers (1, 2, 3) since 1938. Elsom, Bott and Shiels (4) first demonstrated the high degree of activity of the tubules of the dog's kidney in the excretion of organic iodine compounds, and shortly thereafter Elsom, Bott and Walker (5) reported that there was a close correlation between the renal blood flow as measured by the thermostromuhr and the clearance of *Hippuran*. In normal man (3), the average value for plasma diodrast clearance is 688 cc. per 1.73 square meters of body surface area, corresponding to a minimal whole blood flow of 1189 cc. per minute. A readily available means of determining effective renal blood flow in the intact individual is desirable for both physiological and clinical work. However, the general applicability of the procedure has been restricted by the technical difficulties involved in the chemical determination of diodrast.

Diodrast is a synthetic compound which is stated to have the formula 3,5-diiodo-4-pyridone-N-acetic acid diethanolamine, with the following structure:



[1] This work was supported by a grant from the Commonwealth Fund for the study of essential hypertension.

Its molecular weight is 510 and its iodine content is approximately 49.8 per cent.[2]

The estimation of diodrast in biological fluids rests on the determination of the iodine which it contains. Heretofore most of the methods used have been based either upon the alkaline ashing procedure of Kendall (6) or the acid distillation of Leipert (7). These methods were developed primarily for measuring the very low levels of organic iodine normally circulating in the blood, and are laborious and time-consuming even with the more recent modifications. Diodrast-iodine, on the other hand, during experimental procedures, is maintained at levels which are a hundred- to a thousand-fold those of normally occurring iodine. It seemed, therefore, that a less laborious but still accurate method for determining diodrast-iodine would have practical value. Recently White and Rolf (8) have published a simplified procedure which depends on the acid digestion of tungstic acid filtrates, and oxidation with potassium permanganate. However, the large correction factor, about 15 per cent for plasma iodine, allows the possibility of considerable error.

The method to be described here depends upon the observation that bromine oxidizes the iodine of diodrast directly and quantitatively to iodate. The oxidation is performed on filtrates of plasma and urine, after precipitation with zinc hydroxide (Somogyi, 1930 (9)). The iodate is then titrated with sodium thiosulphate.

REAGENTS

Acid Zinc Sulphate Solution (9). 12.5 gm. of $ZnSO_4 \cdot 7\ H_2O$ are dissolved in 125 cc. of 0.25 normal H_2SO_4 and made up to one liter with water.

Sodium Hydroxide, 0.75 Normal. When 50 cc. of the zinc sulphate solution are titrated with 0.75 N NaOH, with phenolphthalein as indicator, 6.7 to 6.8 cc. of the alkali should be required. The solution is shaken vigorously during the titration.

Bromine, C. P. This may be stocked conveniently in a double-glass-stoppered "ether" bottle. For use during the procedure, a smaller dropper bottle is employed.[3]

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[2] The diodrast used in these experiments and the data concerning its chemical composition were kindly supplied by the Winthrop Chemical Company.

[3] This dropper bottle was designed by Dr. Homer W. Smith and is manufactured by E. Machlett and Sons, 220 East Twenty-third Street, New York City.

Sodium Thiosulphate, 0.001 N. A stock 0.1 N solution keeps well for several months in a tightly stoppered dark bottle. The 0.001 N solution used for titration, if protected against light and CO_2, will maintain its strength for several weeks.

Potassium Iodate, 0.1 N, Stock Solution. Since, in the iodometric titration, each molecule of KIO_3 reacts with an excess of KI to liberate six atoms of iodine, then a liter of 0.1 N KIO_3, with a molecular weight of 214.0, is made up to contain $\frac{21.40}{6}$ or 3.567 grams of KIO_3. This solution keeps indefinitely.

Potassium Iodate, 0.001N. This is made up from the 0.1 N stock solution as needed.

Phosphoric Acid (H_3PO_4), C. P. This is kept for use in an ordinary dropper bottle.

Potassium Iodide, 5 per cent solution, is prepared freshly each day or two.

Starch Solution, 1 per cent. This is prepared from Lintner's soluble starch. A clear solution can be obtained by gentle heating with constant rotation and avoidance of boiling. This is made freshly each day or two. Preservatives should not be added.

PROCEDURE

A. Precipitation of proteins

Plasma: The Somogyi procedure is modified by the addition of water prior to the precipitating agents. One volume (3–5 cc.) of plasma (or serum) is pipetted into a 125 cc. Erlenmeyer flask, followed by five volumes of water, eight volumes of Somogyi's zinc sulphate solution, and one volume of 0.75 normal sodium hydroxide. The flask is shaken vigorously after each addition. The precipitate is allowed to stand for thirty to forty minutes before filtration. A fifteen cc. aliquot of the filtrate is equivalent to one cc. of plasma.

Urine: The urine is treated by the standard Somogyi precipitation procedure in order to remove traces of protein and coloring matter which would interfere with the subsequent titration. An aliquot sample of the bladder urine is first accurately diluted to twenty-five times or more of its original volume with water. To one volume of the diluted sample eight volumes of Somogyi's zinc sulphate solution and one volume of 0.75 N sodium hydroxide are added. After shaking thoroughly, the precipitate is allowed to stand thirty to forty minutes, and filtered. A ten cc. aliquot of the filtrate is equivalent to one cc. of diluted urine.

B. Oxidation

Each aliquot sample is pipetted into a 200 mm. x 25 mm. Pyrex test tube. Three drops of phosphoric acid and four or five glass beads are added. To the ten cc. aliquots about five cc. of water are added. In a hood, a drop or two of bromine are added to each tube, which is then boiled over a microburner for five minutes *after* the bromine color has disappeared. The test tubes may be set up conveniently in a row on inclined wire-gauze supports, or in individual clamps. However, each tube *must be started* boiling by hand, with constant shaking. This is necessary because, without constant shaking, the cold bromine settles in droplets at the bottom, and with rapid expansion on heating explodes with loss of fluid. Once boiling begins, the tube is set in its support for the allotted time and the next tube is taken up. Since the total period of boiling is about six minutes for each tube, a rack of six test tube holders can be used in continuous rotation for any number of tubes. The boiling need not be very vigorous and the volume of fluid in each tube should not be allowed to go below seven or eight cc. at any time. If the volume should diminish too rapidly, water may be added in small amounts during the boiling. The tubes are cooled in running tap water. This can be done conveniently in a wire test tube cage large enough for ten or twelve tubes, set in a metal container. The volume of each sample should be returned to about ten or twelve cc. with water before titration.

C. Titration

This can be performed best in a well-lighted cabinet, about 25 x 15 x 12 inches, painted white inside. Care should be taken to eliminate shadows. The end-point of the titration can be sharpened considerably by illuminating the cabinet with a yellow frosted bulb of 40-watt capacity. This produces a gray color in the blue starch-iodine solution, so that one reads the disappearance of density of shadow rather than of color. Judgment as to the precise end-point can also be enhanced by holding, in the same hand with the sample being titrated, a comparison tube containing a similar quantity of water.

Titration is performed with 0.001 N sodium thiosulphate, using a 2.0 cc. self-filling automatic burette, calibrated to 0.01 cc. and fitted

with a very fine pointed tip. The size of each drop can thereby be reduced to about 0.005 cc., and fractions of drops can be delivered by washing them down with water from a fine-tipped dropper. The burette readings are made to 0.001 cc., although the true limit of accuracy of the titration is closer to 0.005 cc. At the beginning of each day's titrations, about 10 cc. of the thiosulphate solution is allowed to run through the burette. This washes out any fluid which may have become changed on standing.

To each sample, just before titration, one cc. of 5 per cent potassium iodide solution is added. When the titration has been carried to the point at which the yellow color of the iodine can no longer be detected, four drops of 1 per cent starch solution are added. This point occurs sooner in the yellow light than in daylight, but no error is introduced by adding the starch early. The titration is continued with frequent vigorous shaking until the solutions in the sample tube and the comparison tube are indistinguishable. The entire titration should be carried out fairly rapidly, adding ten to fifteen drops at a time at the beginning until the density of the shadow begins to clear, then reducing the number of drops progressively until near the end, when only one drop or fraction of a drop should be added at a time. Otherwise the end-point may be easily passed.

D. Calculations

The reactions which take place during the titration are the following:

(1) $$KIO_3 + 5KI + 3H_2O \rightarrow 3I_2 + 6KOH$$

(2) $$3I_2 + 6Na_2S_2O_3 \rightarrow 3Na_2S_4O_6 + 6NaI$$

For each molecule of KIO_3 six atoms of iodine are evolved. Therefore, in terms of these reactions, a normal solution of $Na_2S_2O_3$ is equivalent to a one-sixth molar solution of KIO_3, which contains 21.15 grams of atomic iodine per liter. Hence the 0.001 N $Na_2S_2O_3$ used in the titration is equivalent to a solution containing 2.115 mgm. of I per 100 cc.

Theoretically, in order to determine the concentration of diodrast-iodine in the sample, it should only be necessary to multiply the number of cc. of $Na_2S_2O_3$ used in the titration by the factor 2.115. In actual practice, however, the factor used in the calculation is determined in the following manner:

The strength of the 0.001 N $Na_2S_2O_3$ is determined by titrating 2.0 cc. of 0.001 N KIO_3, to which three drops of H_3PO_4 and 10 cc. of water have been added. The factor (F), expressing 0.001 N $Na_2S_2O_3$ in terms of mgm. per cent of I, is then calculated by means of the following equation in which X equals the number of cc. of 0.001 N $Na_2S_2O_3$ used in the titration.

$$F = 2.115 \times \frac{2.0}{X}$$

In order to avoid the necessity of refilling the burette, the $Na_2S_2O_3$ solution is actually made slightly more concentrated than 0.001 N. Although the strength of the thiosulphate solution, when adequately protected, remains fairly constant for several weeks, the factor (F) is redetermined by titration every 2 or 3 days.

The final calculation of the diodrast-iodine concentration, expressed in mgm. per cent, of each sample of plasma or urine filtrate, is carried out as follows:

mgm. per cent I = F × number of cc. 0.001 N $Na_2S_2O_3$ used in the titration of the sample.

RESULTS

(1) *Recoveries of diodrast-iodine from aqueous solutions.* (Chart I.) When various amounts of diodrast solution corresponding to concentrations of 0.348 to 5.229 mgm. of iodine (I) per 100 cc. were brominated and titrated by the foregoing procedure, the recoveries fell within ±3 per cent of the known value, with the exception of two results at the 5.229 mgm. per 100 cc. level, which showed ±4 per cent deviation. Other determinations, not shown in the chart, up to 10 mgm. per 100 cc. all came within the 3 per cent limit. Table I shows a group of typical recoveries. The agreement between duplicate titrations varied from 0.002 to 0.031 cc. of 0.001 N $Na_2S_2O_3$.

(2) *Recoveries of diodrast-iodine from aqueous solutions after treatment with Somogyi's precipitating agents.* (Chart II.) Solutions of diodrast corresponding to concentrations of iodine varying from 0.174 to 5.229 mgm. of iodine (I) per 100 cc. were treated by the method of *precipitation* described above, brominated and titrated. At levels of 0.5 mgm. per 100 cc. and less there was a definite tendency for the recoveries to be greater than the known values. This may be due

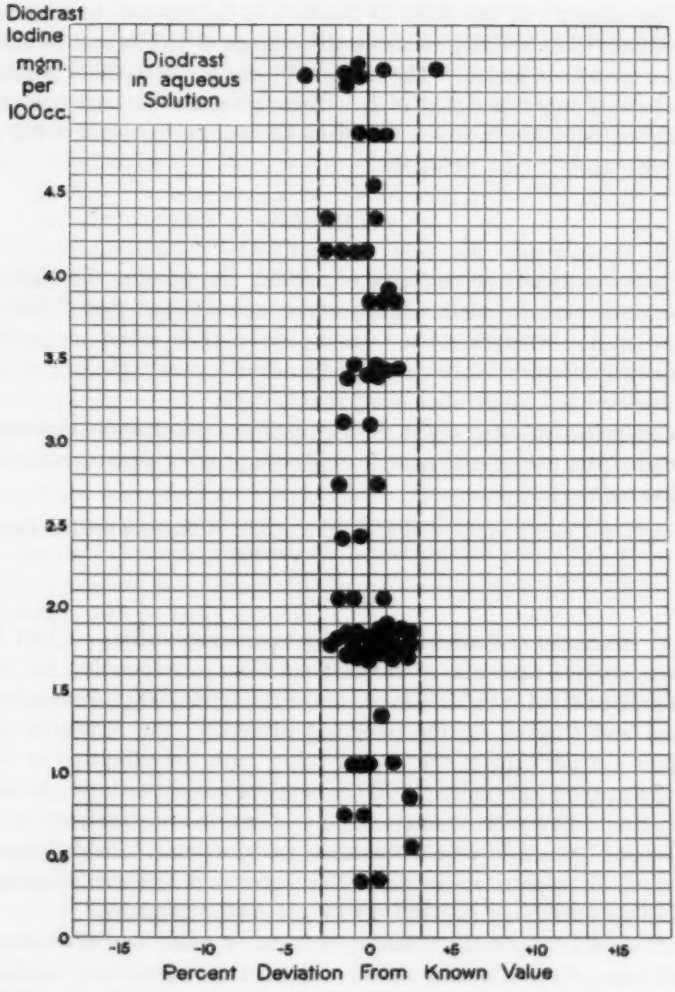

CHART I. Recoveries of diodrast-iodine from aqueous solutions of diodrast. Each point in this and the following charts represents the average of duplicate determinations. The known concentration of diodrast iodine is plotted on the vertical axis.

in part to the fact that at these low levels, overtitration with one or two drops of thiosulphate solution introduces a considerable proportionate error. There may also be some reaction between the precipitating agents and the diodrast, which produces this positive error; none of the reagents themselves produce any detectable iodine when phosphoric acid, potassium iodide and starch solution are added to

TABLE I

Recoveries of Diodrast-Iodine in Aqueous Solution

KNOWN DIODRAST-IODINE CONCENTRATION	DUPLICATE TITRATIONS IN CC. OF 0.001 N $Na_2S_2O_3$ FACTOR = 2.12	AVERAGE DETERMINED VALUE FOR DIODRAST-IODINE CONCENTRATION	DEVIATION OF DETERMINED, FROM KNOWN CONCENTRATION
mgm. per 100 cc.		*mgm. per 100 cc.*	*per cent*
0.348	0.164 0.166	0.349	+0.3
0.522	0.255 0.251	0.535	+2.5
0.870	0.413 0.428	0.890	+2.3
1.044	0.495 0.502	1.056	+1.1
1.743	0.815 0.818	1.733	−0.6
3.486	1.672 1.641	3.515	+0.8
5.229	2.444 2.447	5.184	−0.9

them. At concentrations above 0.5 mgm. of iodine per 100 cc., the recoveries all fell within ±3 per cent of the known value.

(3) *Recoveries of diodrast-iodine from urine.* (Chart III.) When undiluted urine containing no diodrast was brominated, a substance was formed which possessed oxidative or catalytic properties, so that on the addition of KI a variable amount of iodine was liberated. Inasmuch as the concentration of diodrast in the urine under experimental circumstances is high, requiring dilution of twenty-five times

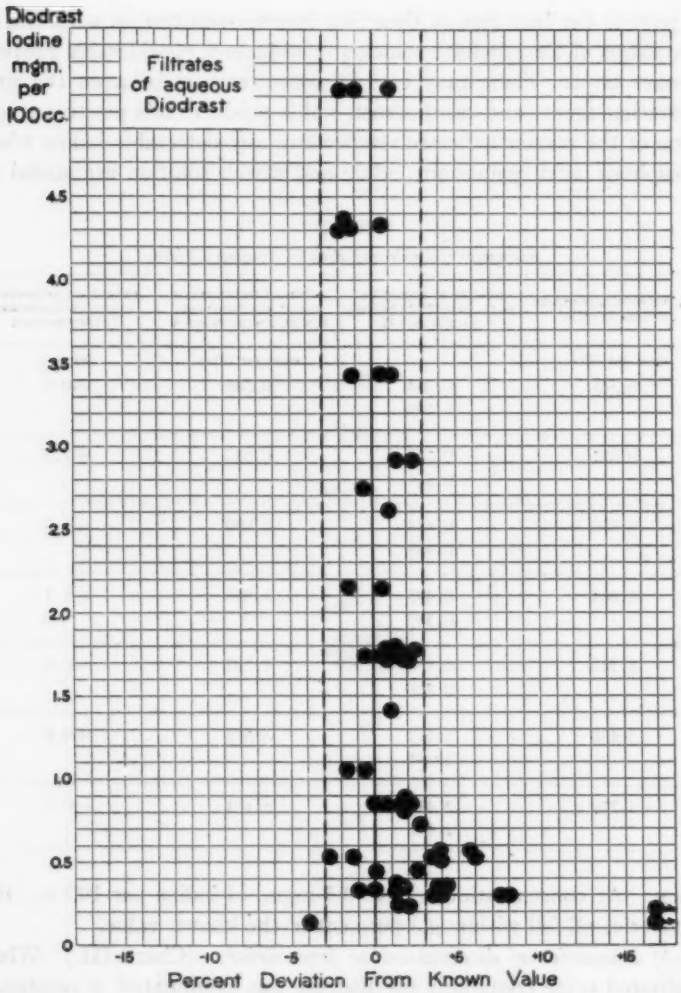

CHART II. Recoveries of diodrast-iodine from filtrates of aqueous solutions of diodrast which had been treated with Somogyi's precipitating agents.

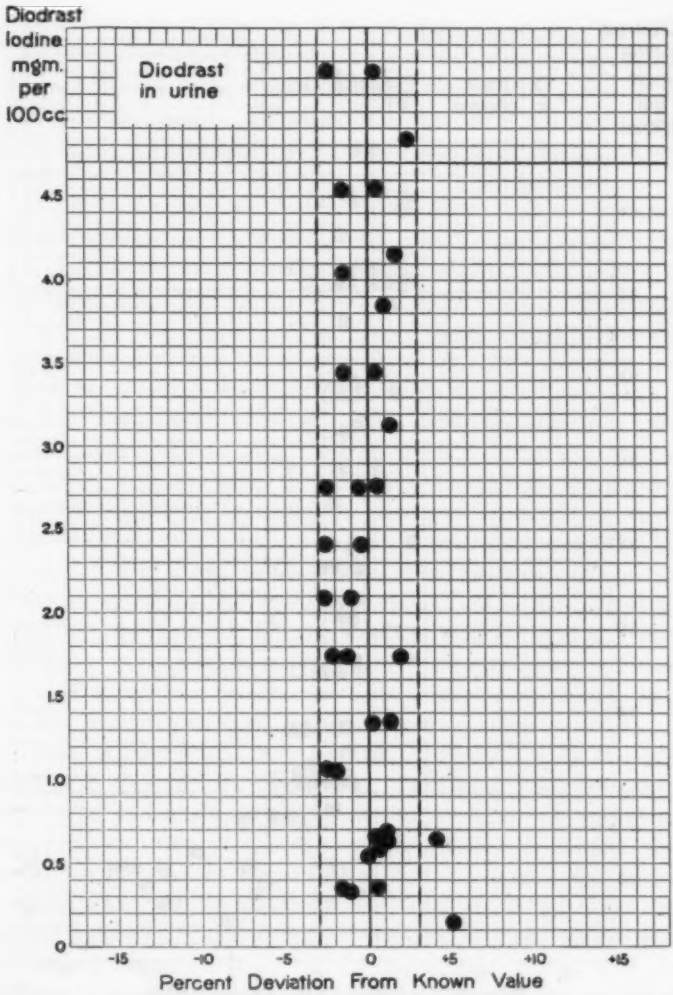

CHART III. Recoveries of diodrast-iodine from diluted human and dog urine to which diodrast had been added. The samples were treated with Somogyi's precipitating agents and filtered.

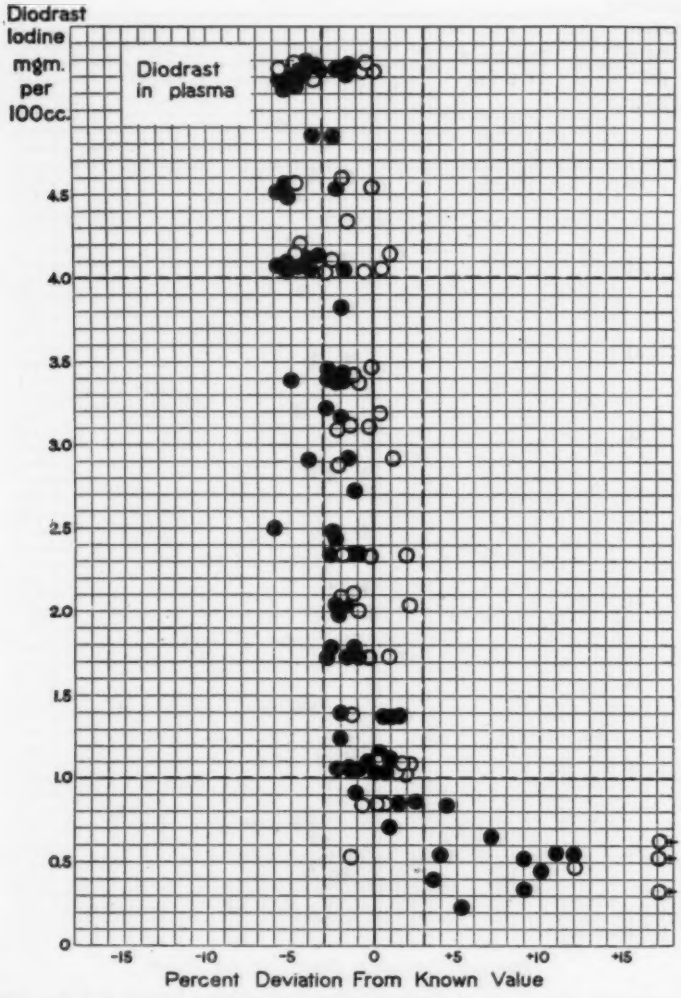

CHART IV. Recoveries of diodrast-iodine from human (solid dots) and dog (open circles) plasma to which diodrast had been added.

or more, samples of urine diluted in a similar manner, were brominated. Under these conditions the concentration of the interfering substances was so low that samples containing no diodrast produced no iodine with potassium iodide. The recoveries from urine diluted twenty-five times, prior to treatment with the precipitating agents (shown in Chart III), come within ±3 per cent of the known values.

(4) *Recoveries of diodrast-iodine from blood plasma.* (Chart IV.) Numerous determinations of diodrast added directly to both human and dog plasma were performed. The recoveries at iodine levels between 1.0 and 4.0 mgm. per 100 cc. were, with a few exceptions, within 3 per cent of the known value. Below 1.0 mgm. per 100 cc. there was a tendency for the results to be greater than the actual values, and above 4.0 mgm. per cent they tended to be too low. The cause for the positive recoveries at the low levels may be in part the same as appeared when aqueous solutions of diodrast were treated by the Somogyi precipitating agents. The question of the presence of oxidative substances in undiluted plasma filtrates, similar to those found in urine, was investigated. Such substances were found only rarely, and then in such small amount that they were reduced by one or two drops of the thiosulphate solution. Since this is within the range of error at normal working levels of diodrast iodine, it was felt that blank determinations for this factor were unnecessary. However, traces of oxidative or catalytic substances may be responsible, in part, for the positive errors at very low levels of diodrast-iodine. The tendency toward significantly less than theoretical recoveries at high diodrast levels is difficult to explain. It did not appear when diodrast was added to filtrates *after* the plasma protein was removed. It was found, also, that when plasma was diluted 15 times or more during precipitation, the tendency toward low recoveries was reduced, whereas, when the plasma was diluted only five or ten times, an increased incidence of low recoveries appeared at lower concentrations of diodrast-iodine.

Table II presents a statistical analysis of the percentage deviation of the recoveries from the known values at different levels of plasma diodrast-iodine concentration. It appears from this that the chance of considerable error at levels below 1.0 mgm. per 100 cc. is so great as to make it inadvisable to work in this range. Between 1.0 and 2.0

mgm. per 100 cc. the lowest mean deviation occurs, indicating that the greatest accuracy may be expected in this range. These levels of diodrast-iodine are the ones most frequently employed in performing determinations of effective renal blood flow. At concentrations of between 2.0 and 4.0 mgm. per 100 cc. the mean deviation is scarcely great enough to require the use of a correction factor in physiological experiments. At concentrations above 4.0 mgm. per 100 cc. it appears to be advisable either to add a correction factor of 3 per cent of the determined value, or to dilute the plasma appropriately, prior to precipitation, to bring the iodine concentration to between 1.0 and 4.0 mgm. per 100 cc.[4]

TABLE II

Statistical Analysis of Data Shown in Chart IV

KNOWN DIODRAST-IODINE CONCENTRATION	NUMBER OF OBSERVATIONS	MEAN DEVIATION OF DETERMINED, FROM KNOWN VALUES	STANDARD DEVIATION OF THE INDIVIDUAL OBSERVATIONS	STANDARD DEVIATION OF THE MEAN
mgm. per 100 cc.		*per cent*	*per cent*	*per cent*
0.174–0.99	21	+6.73	6.14	1.34
1.00 –1.99	26	−0.25	1.47	0.289
2.00 –3.99	38	−1.72	1.53	0.248
4.00 –5.23	41	−3.10	1.83	0.286

SUMMARY

A method is described for the rapid determination of diodrast-iodine in filtrates of plasma and urine. The method is based upon the observation that diodrast-iodine may be oxidized directly by bromine.

The author wishes to acknowledge his indebtedness to Dr. James Bordley, III, for his stimulating criticism and help during the development of the method described in this report; and to Drs. Edwin L. Crosby and Marie N. Cakrtova for their advice and assistance in the statistical analysis of the results.

[4] Although the accuracy of the plasma diodrast-iodine determinations at concentrations above 5.5 mgm. per 100 cc. has not been extensively explored, several determinations at concentrations between 5.8 and 8.7 mgm. per 100 cc. have shown deviations from the known values varying between *minus* 0.9 and *minus* 4.4 per cent (mean deviation *minus* 3.3 per cent). It seems probable, therefore, that the maximum negative deviation is reached at a plasma concentration of approximately 4.0 mgm. per 100 cc.

ADDENDUM

A description of the rapid method for determining diodrast-iodine was forwarded to Dr. Homer W. Smith in February, 1941. Dr. Smith has compared the results

TABLE A

Diodrast-Iodine Determinations on Human Plasma, Comparison of Rapid Method with Fusion Method

DATE	IODINE, MGM. PER 100 CC. OF PLASMA		PERCENTAGE DEVIATION
	Fusion method	Rapid method	
3/31	0.899	1.000	+11.2
3/31	0.916	0.934	+2.0
4/9	1.087	1.07	−1.6
2/22	1.169	1.188	+1.6
2/22	1.169	1.254	+7.3
3/20	1.233	1.263	+2.4
3/20	1.233	1.256	+1.9
3/20	1.233	1.192	−3.3
3/20	1.233	1.172	−5.0
4/7	1.235	1.25	+1.2
4/14	1.238	1.312	+6.0
4/1	1.255	1.296	+3.3
4/16	1.294	1.385	+7.0
4/9	1.302	1.32	+1.4
4/3	1.342	1.383	+3.1
4/14	1.41	1.557	+10.5
4/1	1.411	1.404	−0.5
4/3	1.482	1.465	−1.2
4/7	1.51	1.49	−1.3
4/16	1.547	1.627	+5.2
4/21	1.668	1.694	+1.6
4/21	1.885	1.908	+1.2
4/18	2.397	2.392	−0.2
4/18	2.88	2.83	−1.7
5/14	9.01	9.37	+4.0
5/14	10.55	10.6	+0.5
5/14	14.6	14.46	−1.0
5/7	21.76	21.65	−0.5
5/7	21.95	21.18	−3.5
5/7	24.7	23.85	−3.6
5/16	32.72	32.15	−1.7
5/16	33.12	32.68	−1.3
5/16	36.93	35.63	−3.5

obtained by this method with those obtained by his modification of Kendall's alkaline fusion method (1). Simultaneous analyses were made by both methods upon samples of human plasma and urine obtained in routine determinations of

effective renal blood flow and tubular excretory mass. The results are shown in the accompanying tables (Tables A and B) which were kindly supplied by Dr.

TABLE B

Diodrast-Iodine Determinations on Diluted Human Urine, Comparison of Rapid Method with Fusion Method

DATE	IODINE, MGM. PER 100 CC. OF DILUTED URINE		PERCENTAGE DEVIATION
	Fusion method	Rapid method	
4/7	1.107	1.138	+2.8
4/16	1.126	1.144	+1.6
3/31	1.137	1.153	+1.4
4/14	1.140	1.137	−0.3
4/14	1.160	1.146	−1.2
3/7	1.169	1.136	−2.8
4/9	1.195	1.242	+3.9
4/16	1.202	1.192	−0.8
5/7	1.212	1.200	−1.0
5/7	1.226	1.194	−2.6
4/14	1.250	1.286	+2.9
5/7	1.294	1.285	−0.7
4/16	1.307	1.310	+0.2
3/31	1.335	1.380	+3.4
3/31	1.350	1.445	+7.0
5/7	1.375	1.374	−0.1
4/3	1.377	1.414	+2.7
4/9	1.388	1.383	−0.4
4/7	1.400	1.438	+2.7
4/1	1.428	1.480	+3.6
4/1	1.457	1.522	+4.5
4/9	1.457	1.536	+5.4
4/3	1.490	1.558	+4.6
5/7	1.550	1.542	−0.5
4/1	1.562	1.630	+4.3
4/21	1.563	1.601	+2.4
4/21	1.676	1.763	+5.2
4/3	1.719	1.767	+2.8
4/18	1.800	1.777	−1.3
4/7	1.866	1.935	+3.7
4/21	1.902	2.000	+5.2
4/18	2.380	2.420	+1.7
4/18	2.550	2.545	−0.2

Smith. The cadmium sulphate method* for the precipitation of the plasma proteins was substituted for Somogyi's zinc sulphate method, but the total plasma

* Fujita, A., and Iwataka, D.: *Biochem. Zeitschr.* **242**: 43, 1931.

dilution of 1:15 was maintained. At low iodine levels 15 cc. of filtrate were taken for analysis, while at high iodine levels only 2 cc. were used. The urine samples, all of which were protein-free, were not treated with the precipitating agents but were simply diluted with water to bring the iodine concentration to approximately 1 to 2 mgm. per 100 cc., and 2 cc. of this diluted sample were taken for analysis. A 0.001 N solution of $Na_2S_2O_3$ was used in all titrations, and no correction for a blank was made in either plasma or urine iodine calculation.

The bromine was boiled off from a number of tubes at one time by heating them in a saturated solution of NaCl having a boiling point 104–110°C., the samples being boiled for five minutes after the bromine fumes had disappeared. Glass anti-bumping sticks were used instead of beads.

The mean deviation of the values obtained by the rapid method, from those obtained by the fusion method has been calculated from Tables A and B: (1) Thirty-three observations on plasma samples: mean deviation +1.25 per cent, standard deviation of the mean 0.67 per cent, standard deviation of the individual observations 3.87 per cent. (2) Thirty-three observations on diluted urine samples: mean deviation +1.83 per cent, standard deviation of the mean 0.44 per cent, standard deviation of the individual observations 2.51 per cent. Considering the fact that two variables are being compared, the results obtained by the rapid method appear to agree very favorably with those obtained by the fusion method.

BIBLIOGRAPHY

1. Smith, H. W., Goldring, W., and Chasis, H.: The measurement of the tubular excretory mass, effective blood flow and filtration rate in the normal human kidney. *J. Clin. Invest.*, **17:** 263, 1938.
2. Smith, H. W.: Studies in the Physiology of the Kidney. *Porter Lecture Series, No. 9*, University of Kansas. University Extension Division, Lawrence, Kansas, 1939.
3. Goldring, W., Chasis, H., Ranges, H. A., and Smith, H. W.: Relations of effectual renal blood flow and glomerular filtration to tubular excretory mass in normal man. *J. Clin. Invest.*, **19:** 739, 1940.
4. Elson, K. A., Bott, P. A., and Shiels, E. H.: On the excretion of skiodan, diodrast, and hippuran by the dog. *Am. J. Physiol.*, **115:** 548, 1936.
5. Elson, K. A., Bott, P. A., and Walker, A. M.: The simultaneous measurement of renal blood flow and the excretion of hippuran and phenol red by the kidney. *Am. J. Physiol.*, **118:** 739, 1937.
6. Kendall, E. C.: Determination of iodine in connection with studies in thyroid activity. Third paper, *J. Biol. Chem.*, **43:** 149, 1920.
7. Leipert, T.: Die Bestimmung kleinster Iodmengen in organischem Material. *Biochem. Ztschr.*, **261:** 436, 1933.
8. White, H. L., and Rolf, D.: A rapid micromethod for determining diodrast and inorganic iodide iodine in blood and urine. *Proc. Soc. Exp. Biol. and Med.*, **43:** 1, 1940.
9. Somogyi, M.: A method for the preparation of blood filtrates for the determination of sugar. *J. Biol. Chem.*, **86:** 655, 1930.

CHANGES INDUCED IN PATIENTS WITH HYPERTHYROIDISM BY THE ORAL ADMINISTRATION OF DESICCATED THYROID

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That atrophy of the thyroid gland could be brought about in simple diffuse and nodular colloid goiter as a result of the administration of desiccated thyroid (H. W. & D.) by mouth was reported in 1940.[1] To bring about such a striking change in the histological structure of the thyroid, from that of dilated colloid-containing follicles, to the characteristic microscopic appearance of atrophy, with the small contracted empty follicles, requires the continuous administration of thyroid extract over a period of several months. However, in a much shorter time, the therapeutic effect of the desiccated thyroid was manifested by the steady elevation of the basal metabolic rate, associated with an immediate diminution in the size of the thyroid and an increase in the consistency of the gland. The degree of atrophy of the thyroid seemed to be in direct proportion to the amount of desiccated thyroid given by mouth, and the length of time of its administration. The most complete atrophy of the gland was obtained when a rather marked state of artificial hyperthyroidism was induced. In one patient it was necessary to administer as much as 8 grains of thyroid per day to increase the basal metabolic rate from minus 30 to plus 20. This increase was maintained for one year and produced the most extreme atrophy of the thyroid. This advanced atrophic state was characterized histologically by an almost total disappearance of colloid from the lumen of the follicles; that which remained incompletely filled the latter, and took very little stain. The follicles were reduced in size and number; some were so contracted that their lumina seemed

[1] Rienhoff, W. F.: Microscopic changes induced in thyroid gland by oral administration of desiccated thyroid. *Arch. Surg.*, 41: 487–509, 1940.

to be obliterated, the apices of the lining epithelial cells impinging upon one another. The nuclei of the epithelial cells stained well with hematoxylin, but the cytoplasm remained colorless, as if the protein of the cytoplasm had been washed away. Throughout the stroma there was a marked increase in the number of lymphoid germinal centers and an infiltration of small lymphocytes throughout the parenchyma. Since the follicles were emptied of their colloid and "deflated," there was an apparent increase in the stroma. That the foregoing histological changes were due to progressive atrophy, was shown by repeated biopsies of the thyroid gland before, during and after the administration of desiccated thyroid. The extent of these changes in the structure of the gland is shown in the photomicrographs of the article mentioned above. Reduction in size of large diffuse and nodular colloid goiters has since been accomplished successfully by feeding thyroid. The general condition of the patients was improved, and their basal metabolic rates rose to within normal limits. It is felt that in this group of cases surgical removal of the gland can be avoided.

In view of the atrophy of the thyroid produced by feeding desiccated thyroid to patients with colloid goiters it was believed that it might also be possible to induce atrophy in the stump of tissue remaining after the removal of a hyperplastic gland. Accordingly, for over two years, patients who have been operated upon for hyperthyroidism have been placed upon small postoperative doses of desiccated thyroid. Such treatment has not yet been carried on long enough to permit judgment as to whether it will prevent recurrence of hyperthyroidism. Nevertheless, it has not had a detrimental effect upon the patients.

The present report describes preliminary observations in an attempt to produce atrophy in the hyperplastic goiter of Graves' disease by administering desiccated thyroid, preoperatively.

Nine patients suffering from severe hyperthyroidism have been treated with desiccated thyroid by mouth. In only one of these was the treatment continued for more than three weeks; in that case, it was continued for six months. All of the patients were subjected to operation at the end of the period during which thyroid was given, without resorting to any other medication, such as iodine. In two cases, biopsies were performed before the desiccated thyroid was

given, in order to compare the histological structure of the gland before and after the patient was treated. In one patient over six months intervened between a left and right lobectomy; during this interval the patient received thyroid medication. In all cases, four grains of desiccated thyroid were given daily by mouth in one grain doses. All patients have recovered and have remained well, without any residual clinical signs or symptoms of hyperthyroidism, and with basal metabolic rates within normal limits.

CASE REPORT

Miss C. C., age 46. Typical diffuse goiter with severe hyperthyroidism. Admitted to West Baltimore General Hospital on October 24, 1939. Basal metabolic rate plus 70. Given Lugol's solution; basal metabolic rate dropped to plus 26 after 51 days in hospital. On December 8, 1939, left lobectomy was performed. The patient had a severe postoperative reaction and was discharged at the end of December with persistent hyperthyroidism. The histological appearance of the excised portion of the left lobe of the thyroid, revealed typical hypertrophy and hyperplasia with moderate iodine involution. The clinical condition became worse, with basal metabolic rate ranging between plus 50 and plus 60 for six months. The right lobe became larger, as well as the stump of the left lobe. Loss of weight was progressive, and there were signs and symptoms typical of persistent severe hyperthyroidism. In June, 1940, the patient was placed on one grain of desiccated thyroid by mouth four times each day. After two weeks she stated that she felt much better, less nervous and not as conscious of her heart. The basal metabolic rate after three weeks fell to plus 40 and remained around this level until admission to the Church Home and Infirmary in December, 1940. In July the basal metabolic rate was plus 38, in October plus 39, in November plus 43. After remaining in bed in hospital, but continuing thyroid medication, the basal metabolic rate on December 18, 1940, was plus 33. Symptomatically there was marked improvement. The thyroid gland decreased in size and increased in consistency. On December 21, 1940, right lobectomy was performed. Grossly the gland appeared to be atrophic. There was an elevation of the pulse rate to 130 after operation with a return to normal by the third day. On December 27, six days postoperatively, the basal metabolic rate was plus 15. The patient has remained well since.

The histological structure of the tissue removed at the second operation showed the features characteristic of atrophy of the thyroid: (1) decrease in amount and staining of colloid, (2) decrease in size and apparent number of follicles, (3) increase in stroma, (4) marked increase in lymphocytic infiltration, and (5) decrease in staining of cytoplasm with eosin, so that cell bodies were almost colorless.

This was the first patient with hyperthyroidism treated with desiccated thyroid, and the only one treated for such a long period of time. The patient refused operation at first, and feeling continuously improved clinically, after thyroid medication was begun, was disinclined to return to the hospital for a second operation. The severe reaction after the first operation had so frightened her that it took a long time for her physical and mental status to improve sufficiently for her to consent to the second operation.

The successful outcome of this case led to the use of desiccated thyroid in the preoperative preparation of eight other patients, all with diffuse goiter combined with severe hyperthyroidism. In all patients there was symptomatic improvement after two to four days of treatment, a feeling of less nervousness and palpitation. The basal metabolic rates have in four of the eight patients fallen from plus 100, 72, 60, 55, to plus 40, 22, 27 and 34, respectively. There was a corresponding fall in the pulse rate. These patients received thyroid medication for an average of three weeks before operation. In the remaining four cases the pulse rate fell but the basal metabolic rate remained essentially unchanged. In none of the patients was the basal metabolic rate raised. Although the period of substitution therapy was of short duration the thyroid gland seemed to diminish definitely in size and increase somewhat in consistency. A double partial lobectomy was performed in each of these patients without encountering any difficulties. The thyroid glands were smaller and softer than those usually encountered in patients treated with iodine, and hence were technically less difficult to remove. There was no more postoperative reaction than one would expect in patients treated with iodine. In no instance was there the slightest suggestion of a postoperative thyroid storm.

The period of thyroid medication in these cases was brief (three weeks), and no very definite structural atrophy was noted in the histological examination of the thyroid tissue removed at operation. Previous experience with the cases of colloid goiter had suggested that the histological changes after so brief a period of treatment would not be very striking. It was of particular interest, however, that in the cases in which the basal metabolic rate fell during thyroid medica-

tion, the glands showed none of the colloid involution which is noted in cases treated preoperatively with iodine.[2] One grain of the desiccated thyroid (Hynson, Westcott and Dunning Company) used in the treatment of these patients contains 0.000132 mg. of iodine. This amount of iodine, in itself, is insignificant as far as the treatment of severe hyperthyroidism is concerned.

In a later report the results obtained in these cases will be recorded in greater detail. The explanation of the observed phenomena must await the accumulation of more data. Tentatively it may be suggested that the administration of desiccated thyroid to patients with hyperthyroidism brings about, in some cases at least, a functional atrophy of the thyroid gland. It is of particular interest that in none of the nine patients treated with desiccated thyroid, were the symptoms of hyperthyroidism made worse.

Whether these observations will have any practical clinical significance remains to be seen. It is not the intention of this report to suggest that desiccated thyroid should be used in the routine preoperative treatment of patients with hyperthyroidism.

SUMMARY

Nine patients with hyperthyroidism have been treated preoperatively with desiccated thyroid. Such treatment has not aggravated the hyperthyroidism but on the contrary has tended to bring about a reduction in the signs and symptoms of the disease. There is evidence to suggest that in at least one of the cases the thyroid medication resulted in structural atrophy of the thyroid gland. All of the patients did well postoperatively.

[2] Rienhoff, W. F.: The histological changes brought about in cases of exophthalmic goiter by the administration of iodine. *Bull. Johns Hopkins Hosp.* **37**: 285, 1925.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Medical Microbiology. By KENNETH L. BURDON. 763 pp. Illus. $4.50. *The Macmillan Company, New York, 1939.*

There is much to be said in favor of a course in Microbiology both in Undergraduate Schools and in Medical Schools. Especially in Medical Schools which may not have separate departments of Bacteriology, Protozoology and Mycology and in which the time schedule does not permit separate courses in each of these subjects, a department and course in Microbiology might more adequately meet the requirements of the students.

The general plan of Dr. Burdon's book is excellent and the material is interestingly presented but a reading of the book leaves one suspended between Undergraduate School and Medical School. In the opinion of the reviewer the emphasis on medical microbiology is not justified for an undergraduate course and the book is not adequate for a course in Microbiology in the Medical School. It would seem better if the subject were divided; General Microbiology for the Undergraduate School, and Medical Microbiology for the Medical School. The task of teaching Medical Microbiology to medical students would be much easier if they had received adequate training in the technique and principles of General Microbiology in their undergraduate education.

The book would be profitable reading as a means of orientation for students about to enter Medical School or as supplemental reading in Medical School. It is disturbing to note statements in the text without reference to original sources. The list of "Sources of Information about Microbiology" in Appendix D is largely to text-books or books of a general character. Text-book teaching is not highly regarded by the reviewer.

J. H. B.

Edinburgh Post-Graduate Lectures in Medicine. Vol. 1, 1938–39. 513 pp. Illus. 15/6d. *Published for the Honyman Gillespie Trust by Oliver and Boyd, Edinburgh and London, 1940.*

"The Edinburgh Post Graduate Lectures In Medicine" established to promote post-graduate teaching gratis to practitioners and students of medicine comprise thirty-three lectures on a series of topics of great diversity.

Each is presented with clarity, simply and in an authoritative fashion. None is without interest or without a kernel of wise instruction, and few lack a work-a-day datum of helpfulness to the practitioner. Though admittedly the text of each presentation is intended primarily for the average physician, technical matters

are not overly simplified and the original sources of many matters are given so that the reader may readily search for more information.

Neurology, psychiatry, urology, endocrinology, cardiology, oncology, surgery and internal medicine are all represented in the subject-matter, and in such a way as to commend the collated material to the readers or listeners for whom they were composed.

C. R. A.

Applied Pharmacology. By HUGH ALISTER MCGUIGAN. 914 pp. Illus. $9.00. *C. V. Mosby Company, St. Louis, 1940.*

From the view point of the clinician, it is desirable to have a textbook which provides a presentation of experimental pharmacology and its contributions to the understanding of the mechanisms concerned in disease states, and to the scientific and intelligent treatment of human diseases. In the preface, the author states that the object of this book is to connect physiology, biochemistry, and pharmacology with clinical applications, and that without this clinical view in mind pharmacology becomes a morbid curiosity. Such a task to be undertaken by one man who is essentially a pharmacologist is necessarily difficult unless he is at the same time in active contact with the clinic. Although this book contains much valuable information, it falls far short of its purpose and affords little of value to the clinician, which cannot be obtained in other standard texts of pharmacology. The discussion of so many of the important clinical substances such as liver, insulin, iron, cortical hormones, and the sulfonamides is inadequate, while several pages are devoted, for instance, to veratrine, aconite and related substances.

There are certain omissions. None of the clinically important derivatives of acetylcholine, such as acetyl-beta-methyl choline and carbaminoyl choline, is mentioned although three pages are devoted to formaldehyde. Desoxycorticosterone therapy is not included and the latest reference in relation to adrenal pharmacology is 1936.

In general, the content of pharmacology in its more restricted sense is well covered, and although the book will probably not find many clinical uses, it may serve as a useful text for students of pharmacology.

A. M. H.

Das Hospital zu St. Georg in Leipzig durch acht Jahrhunderte, 1212–1940. 1. Band. Das Hospital zu St. Georg vom Jahre 1212 bis zum Jahre 1631. By PROF. DR. C. SEYFARTH. 249 pp. Illus. 10 Reichsmarks (paper bound). 11 Reichsmarks (bound). *Georg Thieme, Leipzig, 1939.*

This volume, dealing with the first four centuries of the St. Georg Hospital in Leipzig, is a very careful and detailed study by its present physician-in-chief. The book tells not only of the buildings, the patients, and physicians, but also of the management of the hospital, its revenues, and expenses, revealing an interesting aspect of medieval life.

Like so many other hospitals, St. Georg was founded in connection with a

monastery and at first served as an abode for pilgrims, travelers, and poor and sick people. In 1439 it was taken over by the city and the care of the sick gradually became its main though not exclusive object. At first the members of the medical faculty visited the sick inmates, and the attendant of the bathhouse treated the surgical cases. From the late fifteenth century on the town barber usually served as hospital surgeon, and somewhat later we also find salaried physicians. The majority of the patients came from the poor of the city, but occasionally well-to-do people took advantage of it too. Various guilds had contracts with the hospital whereby the latter had to take care of their members, particularly journeymen and apprentices.

It is interesting to see that mental cases were frequent and were segregated in a separate house only if they became violent. This, as the author rightly emphasizes, shows that the insane were not always treated as possessed. Lepers were not accepted. The food consisted of great amounts of meat, bread, and vegetables, beer being the usual beverage.

The hospital was destroyed twice during the religious wars, first in 1547, then again in 1631, the date with which the present first volume ends.

The book is clearly written and can be recommended as an important contribution to the older history of medicine, hygiene, and public health.

O. T.

Psychobiology and Psychiatry. By WENDELL MUNCIE. 739 pp. Illus. $8.00. *C. V. Mosby Company, St. Louis, 1939.*

Dr. Muncie has assembled in his Psychobiology and Psychiatry, a clear and comprehensive statement of the teachings of Adolf Meyer. It was written according to Dr. Meyer's prefatory statement "out of concrete practice, a free upshot from his actual diagnostic and treatment work and teaching in our hospital." "It is a voice from a workshop, making articulate . . . the mode of working, inquiring, and sharing practiced for the whole of man and his setting and not only the parts of man."

Dr. Muncie has faithfully reported the methodology of the work at the Phipps Psychiatric Clinic. The whole emphasis is upon the total personality, as an integrate of the various anatomical, physiological, psychological, and social structures.

The book therefore fittingly opens with a discussion of normal personality and the methods of its study. The course for the student by which he can analyze his own personality is given. This is planned to lead the student into the same type of study for his psychiatric patient.

The intermediate portion of the book is devoted to the technique of examination and is followed by a discussion of the various reaction types met in psychiatry. The cases are clearly illustrative, and have the great virtue of being presented as a series of facts without a mass of interpretative theorizing.

The student, as well as the psychiatric practitioner, will indeed welcome this presentation. Nowhere in the volume is there any dogmatism. The criticisms of other "schools" have been clearly stated and admitted. The answers are direct

and space for the future development of psychiatry is indicated. One might sum up the volume by saying we have an intelligent, eclectic survey of various routes into a continent in which much exploration is needed.

L. B. H.

Cancer of the Larynx. By CHEVALIER JACKSON and CHEVALIER L. JACKSON. 309 pp. Illus. $8.00. *W. B. Saunders Company, Philadelphia, 1939.*

In this work the authors have made available to the medical profession both a text and a reference book. The great experience of the authors with laryngeal disease makes their ideas particularly weighty.

There are thirty-one chapters which cover every known aspect of the subject. The ideas which the authors wish to advance are put forth clearly and concisely. The bibliography is very complete. The illustrations are well chosen. The five colored plates (paintings of the larynx, normal and pathological views) with their explanations are interesting and instructive.

For those working on, or interested in, diseases of the larynx, this work is essential.

E. N. B.

Diagnosis and Treatment of Arthritis and Allied Disorders. By H. M. MARGOLIS. 551 pp. $7.50. *Paul B. Hoeber, New York, 1941.*

This is a complete and well written book. The introductory chapter includes important facts concerning the socio-economics of arthritis. We are reminded that this malady is nearly twice as common as any other single disease; that it results in the loss of a quarter of a billion dollars of working time in this country each year; that there are very inadequate hospital facilities for the care of arthritic patients, who comprise 5 per cent of our total population.

Following a useful, and generally accepted outline of classification of the arthritides, the author discusses in detail the individual types of arthritis beginning with the more common forms. At the end of each section there is a bibliography which is particularly helpful in providing reference to the less usual forms of arthritis, which are not discussed extensively. Throughout the book there are numerous splendid illustrations showing the clinical and pathological appearance and x-ray changes in the various types of affected joints. In the section on medical management, there is an up-to-date, brief, accurate discussion of the use of gold salts in the treatment of atrophic (rheumatoid) arthritis. A considerable amount of space is devoted to the orthopedic care of arthritis; and the discussion clearly indicates the need for united effort by medical practitioner and orthopedic surgeon in the management of most forms of arthritis.

This book is valuable for those intending to use the newer methods of treatment, where the success of therapy depends upon the exact type of arthritis being treated; (2) for the practicing physician to whom the management of arthritis has always been a great problem; (3) for the medical student who frequently complains of inadequate teaching in this subject.

T. M. B.

BOOKS RECEIVED FOR REVIEW

A Surgeon Explains to the Layman. By M. BENMOSCHÉ. 317 pp. Illus. $3.00. *Simon and Schuster, New York, 1940.*

In Search of Complications. An Autobiography by EUGENE DE SAVITSCH, M.D. 396 pp. $3.00. *Simon and Schuster, New York, 1940.*

Diagnosis and Treatment of Arthritis and Allied Disorders. By H. M. MARGOLIS. 551 pp. Illus. $7.50. *Paul B. Hoeber, New York, 1941.*

Doctrina y Práctica de la Profilaxis de la Tuberculosis. By LUIS SAYÉ. 355 pp. Illus. *Editorial Sudamericana, Buenos Aires, [1940].*

Clinical Pellagra. By SEALE HARRIS. 494 pp. Illus. $7.00. *C. V. Mosby Company, St. Louis, 1941.*

The Pharmacological Basis of Therapeutics. By LOUIS GOODMAN and ALFRED GILMAN. 1383 pp. Illus. $12.50. *The Macmillan Company, New York, 1941.*

Debatable Tumours in Human and Animal Pathology. By W. F. HARVEY, E. K. DAWSON, and J. R. M. INNES. 124 pp. 40 plates. 10 sh. 6 d. *Oliver and Boyd, Edinburgh and London, 1940.*

Electrocardiography in Practice. By ASHTON GRAYBIEL and PAUL D. WHITE. 319 pp. Illus. $6.00. *W. B. Saunders Company, Philadelphia and London, 1941.*

Feeding our Old Fashioned Children. By C. ANDERSON ALDRICH and MARY M. ALDRICH. 112 pp. Illus. $1.75. *The Macmillan Company, New York, 1941.*

What Price Alcohol? By ROBERT S. CARROLL. 362 pp. $3.00. *The Macmillan Company, New York, 1941.*

The Care of the Psychiatric Patient in General Hospitals. By FRANKLIN G. EBAUGH. 79 pp. *American Hospital Association, Chicago, 1940.*

Macleod's Physiology in Modern Medicine. Edited by PHILIP BARD. 9th ed. 1256 pp. Illus. $10.00. *C. V. Mosby Company, St. Louis, 1941.*

Introduction to Dermatology. By RICHARD L. SUTTON and RICHARD L. SUTTON, JR. 4th ed. 904 pp. Illus. $9.00. *C. V. Mosby Company, St. Louis, 1941.*

Hemorrhagic Diseases. Photo-Electric Study of Blood Coagulability. By KAARE K. NYGAARD. 320 pp. Illus. $5.50. *C. V. Mosby Company, St. Louis, 1941.*

The Medical Reports of John Y. Bassett, M.D., the Alabama Student. With an Introduction by DANIEL C. ELKIN. 62 pp. Illus. *Charles C. Thomas, Springfield, Ill., 1941.*

Anatomy and Physiology Laboratory Guide. By EDMOND J. FARRIS. 144 pp. Illus. $1.60. *J. B. Lippincott Company, Philadelphia, 1941.*

Medicine and Human Welfare. By HENRY E. SIGERIST. 145 pp. Illus. $2.50. *Yale University Press, New Haven, 1941.*

Age Morphology of Primary Tubercles. By HENRY C. SWEANY. 265 pp. Illus. $5.00. *Charles C. Thomas, Springfield, Illinois, 1941.*

INDEX TO VOLUME LXVIII

Pagination According to Months:

January, 1941, pp. 1–118
February, 1941, pp. 119–202
March, 1941, pp. 203–290
April, 1941, pp. 291–351
May, 1941, pp. 352–423
June, 1941, pp. 425–547

Abel, John Jacob, A Portrait 119
Abscesses, subcutaneous, Multiple self-inflicted 409
Alpert, Louis K.: A rapid method for the determination of diodrast iodine in blood and urine 522
Argyll Robertson pupil, Clinical observations on the pupillary phenomena resulting from regeneration of the third nerve with especial reference to the 309

Baber, Margaret (see Josephs, Hugh W.) 375
Bloch, Oscar: Loss of virulence of treponema pallidum in citrated blood at 5°C. 412
Blood flow to the forearm and calf. I. Vasomotor reactions: Role of the sympathetic nervous system 428
Blood flow to the forearm and calf. II. Reactive hyperemia: Factors influencing the blood flow during the vasodilatation following ischemia 450
Blood flow to the forearm and calf. III. The effect of changes in the arterial pressure on the blood flow to limbs under controlled vasodilatation in normal and hypertensive subjects 477
Blood flow to the forearm and calf. IV. Thyroid activity: Observations on the relation of blood flow to basal metabolic rate 512
Bodian, David, and Howard A. Howe: Experimental studies on intraneural spread of poliomyelitis virus 248
Bodian, David, and Howard A. Howe: Neutropism and the genesis of cerebral lesions in poliomyelitis: An experimental study 58
Book reviews 116, 200, 283, 421, 543
Bratton, A. Calvin (see Marshall, E. K.) 94

Carcinoma, prostatic, Unusual ureteral extension of 337
Celebration of the sixtieth anniversary of Dr. William H. Howell's graduation from the Johns Hopkins University 291
Conn, Howard (see Josephs, Hugh W.) 375
Coronary circuit, Observations on the morphology and functions of some of the components of the 353
Curtis, Harry (see Gay, Leslie N.) 179

Digestive complaints, "Personality disorders" causing 203
Diodrast iodine in blood and urine, A rapid method for the determination of 522
Diseker, Thomas H. (see Turner, Thomas B.) 269

Edwards, Lydia B. (see Marshall, E. K.) 94
Eichna, L. W., and Robert W. Wilkins: Blood flow to the forearm and calf. II. Reactive hyperemia: Factors influencing the blood flow during the vasodilatation following ischemia 450
Eichna, L. W., and Robert W. Wilkins: Blood flow to the forearm and calf. IV. Thyroid activity: Observations on the relation of blood flow to basal metabolic rate 512
Eichna, L. W. (see Wilkins, Robert W.) 428
Eichna, L. W. (see Wilkins, Robert W.) 477
Electricity, Injury due to. A result of contact with 2400 volt circuit; report of an unusual case 388
Electroencephalogram, Eye movements in the 1
Estrin, Influence of, on callous formation 238

Ford, F. R., F. B. Walsh, and A. King: Clinical observations on the pupillary phenomena resulting from regeneration of the third nerve with especial reference to the Argyll Robertson pupil 309

Gay, Leslie N., Harry Curtis, and Theodore Norris: A pollen survey of the islands of Bermuda 179
Gemmill, Chalmers L.: The effects of glucose and of insulin on the metabolism of the isolated diaphragm of the rat 329
Gemmill, Chalmers L., and Louis Hamman: The effects of insulin on glycogen deposition and on glucose utilization by isolated muscles 50
Glycogen deposition and glucose utilization by isolated muscles, The effect of insulin on 50

Hamman, Louis (see Gemmill, Chalmers L.) 50
Harvey, A. M., and R. L. Masland: A method for the study of neuromuscular transmission in human subjects 81
Haviland, James W.: Type I pneumococcal pneumonia 32
Heart, Alterations in the, accompanying growth and hypertrophy 363
Hellman, L. M. (see Maumanee, A. E.) 158
Hesser, Frederick H.: A result of contact with 2400 volt circuit: report of an unusual case 388
Higgins, William H., III: Unusual ureteral extension of prostatic carcinoma 327
Hills, Ralph G., and J. Arthur Weinberg: Influence of estrin on callous formation 238
Howe, Howard A. (see Bodian, David) 248
Howe, Howard A. (see Bodian, David) 58
Howell, William H.: Celebration of the sixtieth anniversary of Dr. William H. Howell's graduation from the Johns Hopkins University 291
Hyperparathyroidism, Nephrocalcinosis and hypertension following; terminal dissecting aneurysm 319
Hyperthyroidism, Clinical and microscopic changes induced in patients with, by the oral administration of desiccated thyroid tablets 538

Johns Hopkins Medical Society, Proceedings of the meeting of.... 112, 196, 280, 347, 416
Josephs, Hugh W., Margaret Baber, and Howard Conn: Studies in vitamin A. Relation of blood level and adaptation to dim light to diet..... 375

King, Arthur B.: Visceral pain in cases of situs inversus..... 169
King, A. (see Ford, F. R.)..... 309
Klein, Arthur: Multiple self-inflicted subcutaneous abscesses..... 409

Lamson, Paul D.: John Jacob Abel, a portrait..... 119
Lyman, Richard S.: Eye movements in the electroencephalogram..... 1

Marshall, E. K., A. Calvin Bratton, Lydia B. Edwards, and Ethel Walker: Sulfanilylguanidine in the treatment of acute bacillary dysentery in children..... 94
Masland, R. L. (see Harvey, A. M.)..... 81
Maumanee, A. E., L. M. Hellman, and L. B. Shettles: Factors influencing plasma prothrombin in the newborn infant..... 158
Mayer, Sidney, Jr.: Nephrocalcinosis and hypertension following hyperparathyroidism; terminal dissecting aneurysm..... 319
Metabolism of the isolated diaphragm of the rat, Effects of glucose and of insulin on the..... 329

Neuromuscular transmission in human subjects, A method for the study of..... 81
Norris, Theodore (see Gay, Leslie N.)..... 179

Oppenheimer, Ella H.: The lowering of blood uric acid by uricase injections..... 190

Pneumonia, pneumococcal, Type I..... 32
Poliomyelitis, Neutropism and the genesis of cerebral lesions in: An experimental study..... 58
Poliomyelitis virus, Experimental studies on intraneural spread of..... 248
Pollen survey of the islands of Bermuda..... 179
Prothrombin, plasma, in the newborn infant, Factors influencing..... 158

Rienhoff, William Francis, Jr.: Clinical and microscopic changes induced in patients with hyperthyroidism by the oral administration of desiccated thyroid tablets.. 538
Robinson, G. Canby: "Personality disorders" causing digestive complaints..... 203

Shettles, L. B. (see Maumanee, A. E.)..... 158
Situs inversus, Visceral pain in cases of..... 169
Sulfanilylguanidine in the treatment of acute bacillary dysentery in children..... 94

Treponema pallidum, Duration of infectivity of, in citrated blood stored under conditions obtaining in blood banks..... 269
Treponema pallidum, Loss of virulence of, in citrated blood at 5°C..... 412
Turner, Thomas B., and Thomas H. Diseker: Duration of infectivity of treponema pallidum in citrated blood stored under conditions obtaining in blood banks.... 269

Uric acid, blood, The lowering of, by uricase injections..... 190

Vitamin A, Studies in. Relation of blood level and adaptation to dim light to diet.. 375

Walker, Ethel (see Marshall, E. K.)..... 94
Walsh, F. B. (see Ford, F. R.)..... 309
Wearn, Joseph T.: Alterations in the heart accompanying growth and hypertrophy.. 363
Wearn, Joseph T.: Observations on the morphology and functions of some of the components of the coronary circuit..... 353
Weinberg, J. Arthur (see Hills, Ralph G.)..... 238
Wilkins, Robert W., and L. W. Eichna: Blood flow to the forearm and calf. I. Vasomotor reactions: role of the sympathetic nervous system..... 425
Wilkins, Robert W., and L. W. Eichna: Blood flow to the forearm and calf. III. The effect of changes in the arterial pressure on the blood flow to limbs under controlled vasodilatation in normal and hypertensive subjects..... 477
Wilkins, Robert W. (see Eichna, L. W.)..... 450
Wilkins, Robert W. (see Eichna, L. W.)..... 512

BRIEF HISTORICAL NOTES ON MEAD'S CEREAL AND PABLUM

HAND in hand with pediatric progress, the introduction of Mead's Cereal in 1930 marked a new concept in the function of cereals in the child's dietary. For 150 years before that, since the days of "pap" and "panada," there had been no noteworthy improvement in the nutritive quality of cereals for infant feeding. Cereals were fed principally for their carbohydrate content.

The formula of Mead's Cereal was designed to supplement the baby's diet in minerals and vitamins, especially iron and B_1. How well it has succeeded in these functions may be seen from two examples:

(1) As little as one-sixth ounce of Mead's Cereal supplies over half of the iron and more than one-fifth of the vitamin B_1 minimum requirements of the 3-months-old bottle-fed baby. (2) One-half ounce of Mead's Cereal furnishes all of the iron and two-thirds of the vitamin B_1 minimum requirements of the 6-months-old breast-fed baby.

That the medical profession has recognized the importance of this contribution is indicated by the fact that cereal is now included in the baby's diet as early as the third or fourth month instead of at the sixth to twelfth month as was the custom only a decade or two ago.

In 1933 Mead Johnson & Company went a step further, improving the Mead's Cereal mixture by a special process of cooking, which rendered it easily tolerated by the infant and at the same time did away with the need for prolonged cereal cooking in the home. The result is Pablum, an original product which offers all of the nutritional qualities of Mead's Cereal, plus the convenience of thorough scientific cooking.

During the last ten years, these products have been used in a great deal of clinical investigation on various aspects of nutrition, which have been reported in the scientific literature.

Many physicians recognize the pioneer efforts on the part of Mead Johnson & Company by specifying Mead's Cereal and PABLUM.

Pablum is a palatable mixed cereal food, vitamin and mineral enriched, composed of wheatmeal (farina), oatmeal, cornmeal, wheat embryo, beef bone, brewers' yeast, alfalfa leaf, sodium chloride, and reduced iron.